Clinics Review Articles

Neurologic Clinics

NEUROCRITICAL CARE

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ELSEVIER

February 2025

Neurocritical Care

Editor

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NEUROLOGIC CLINICS

www.neurologic.theclinics.com

Consulting Editor
RANDOLPH W. EVANS

February 2025 • Volume 43 • Number 1

ELSEVIER

1600 John F. Kennedy Boulevard • Suite 1800 • Philadelphia, Pennsylvania, 19103-2899

http://www.theclinics.com

NEUROLOGIC CLINICS Volume 43, Number 1
February 2025 ISSN 0733-8619, ISBN-13: 978-0-443-13073-1

Editor: Stacy Eastman
Developmental Editor: Varun Gopal

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Neurologic Clinics (ISSN 0733-8619) is published quarterly by Elsevier Inc., 360 Park Avenue South, New York, NY 10010–1710. Months of issue are February, May, August, and November. Periodicals postage paid at New York, NY, and additional mailing offices. Subscription prices are $367.00 per year for US individuals, $100.00 per year for US students, $454.00 per year for Canadian individuals, $514.00 per year for international individuals, $210.00 for foreign students/residents, and $100.00 for Canadian students/residents. For institutional access pricing please contact Customer Service via the contact information below. To receive student/resident rate, orders must be accompanied by name of affiliated institution, date of term, and the *signature* of program/residency coordinator on institution letterhead. Orders will be billed at individual rate until proof of status is received. Foreign air speed delivery is included in all *Clinics* subscription prices. All prices are subject to change without notice. Orders, claims, and journal inquiries: Please visit our Support Hub page https://service.elsevier.com for assistance.

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Neurologic Clinics is also published in Spanish by Nueva Editorial Interamericana S.A., Mexico City, Mexico.

Neurologic Clinics is covered in *Current Contents/Clinical Medicine, MEDLINE/PubMed (Index Medicus), EMBASE/Excerpta Medica, and PsycINFO, and ISI/BIOMED*.

Printed in the United States of America.

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Delirium is not a harmless transient event during ICU hospitalization; rather, it is a severe complication of critical illness associated with increased mortality, morbidity, and persistent disability. Despite being recognized for decades, it remains underdiagnosed. Employing validated tools for detection helps reduce missed cases. Early detection facilitates prompt management. Sedatives, opioids, and antipsychotics should be avoided whenever possible. Optimizing environmental triggers, minimizing iatrogenicity, and treating underlying critical illness constitute the basis of the currently recommended approach to diminish the burden of delirium in ICU patients.

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Preface

The Explosive and Exciting Growth of Neurocritical Care

Alejandro A. Rabinstein, MD
Editor

Since I started my career in Neurocritical Care now almost 25 years ago, the specialty has had enormous growth. Across the United States, we now have a wealth of capable Neurocritical Care teams, dedicated Neurocritical Care units, a large number of fellowship programs accredited by the Accreditation Council for Graduate Medical Education, a very active professional society, and a multidisciplinary board examination sponsored by the American Board of Psychiatry and Neurology and cosponsored by all other pertinent professional boards. Alongside the rapid growth of our specialty, there has been an equally rapid accumulation of knowledge across all aspects of Neurocritical Care. The articles in this issue reflect that growth and elegantly summarize the state-of-the-art in most of the main topics related to the practice of Neurocritical Care, including delirium, status epilepticus and electroencephalographic monitoring, traumatic brain injury, subdural hemorrhage, anoxic encephalopathy, acute ischemic stroke, subarachnoid hemorrhage, intracerebral hemorrhage, and posterior reversible encephalopathy syndrome. The issue concludes with a visionary article on the applications of Artificial Intelligence to the practice and teaching of Neurocritical Care.

The authors of these articles are experts in the field, and I am indebted to them for their dedication to the completion of this issue. I am convinced that these articles deserve the attention of any clinician devoted to the care of neurocritically ill patients. They provide not only an updated review of the literature but also plenty of clinical advice derived from experience at the bedside. And that knowledge is invaluable.

Neurol Clin 43 (2025) xi–xii
https://doi.org/10.1016/j.ncl.2024.10.001
0733-8619/25/© 2024 Published by Elsevier Inc.

DISCLOSURES

The author declares membership in the Independent Event Adjudication Committee for clinical trials for Boston Scientific and Advisory Board meeting participation for Chiesi, Shionogi, Astra Zeneca, and Ceribell.

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ICU Delirium

Amra Sakusic, MD, PhD[a,b,*], Alejandro A. Rabinstein, MD[b,c]

KEYWORDS

• ICU delirium • Critical illness • Iatrogenicity
• Predisposing and precipitating risk factors

KEY POINTS

- Delirium is a common, serious, and often unrecognized complication of critical medical or surgical illnesses.
- The use of standardized validated tools for early ICU delirium detection should be incorporated into routine daily practice.
- Early detection enables timely exploration of underlying causes and facilitates appropriate management.
- Antipsychotics and sedatives should only be used for control of agitation.
- Optimizing environmental conditions, minimizing iatrogenic causes, and effectively managing the underlying illness are essential to reduce the burden of delirium in the ICU.

INTRODUCTION

Awareness of delirium in the critically ill has grown exponentially over the last couple of decades. Yet, this serious complication of critical illness remains underrecognized and insufficiently understood. In this article, we will review the definition, epidemiology, etiology and proposed pathophysiology, clinical presentation, management, and prognostic implications of delirium in the ICU.

DEFINITION

ICU Delirium encompasses a variety of symptoms that arise from generalized brain dysfunction occurring in the context of acute illness or drug intoxication. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[1] outlines several criteria necessary for diagnosing delirium.

- Disturbance in attention and awareness that develops over a short period and represents an acute change from baseline.

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Neurol Clin 43 (2025) 1–13
https://doi.org/10.1016/j.ncl.2024.07.001 **neurologic.theclinics.com**
0733-8619/25/Published by Elsevier Inc.

- Fluctuation of attention and awareness throughout the day.
- Disturbance in cognition including impaired memory, disorientation, visual-spatial disturbance, and impairment of perception.
- Above-mentioned symptoms cannot be explained by a pre-existing neurocognitive disorder and cannot occur in the setting of a coma.
- Adequate evidence from history, physical examination, and laboratory investigations that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal.

EPIDEMIOLOGY

Delirium is a common clinical problem. Between 10% to 16% of patients in the emergency department present with delirium,[2] while approximately 14% to 56% of hospitalized patients develop delirium at some point during hospitalization.[3] A meta-analysis of 48 studies in adult ICUs estimated a pooled prevalence of 31%,[4] but delirium has been reported to affect up to 82% of critically ill patients on mechanical ventilation.[5] Yet, the reported prevalence of delirium across different ICU cohorts has been considerably variable even among cohorts with similar measures of severity of illness. Such discrepancies signal major differences in the sensitivity of diagnosis of delirium across ICUs worldwide.

PATHOPHYSIOLOGY

The pathophysiological mechanisms underlying ICU delirium remain largely unknown. Various theories have been proposed, attributing its occurrence to impaired cerebral blood flow, neurotransmitter imbalances, genetic abnormalities, disruption of the blood-brain barrier, or exacerbated brain inflammation.[6–8] Abnormal synthesis, release, and inactivation of multiple neurotransmitters, including gamma-aminobutyric acid, acetylcholine, dopamine, and serotonin, may contribute to delirium development.[9] Meanwhile, elevated levels of proinflammatory cytokines, such as C-reactive protein and procalcitonin, that are commonly observed during acute critical illness may disrupt the blood-brain barrier, initiating a cascade of events that can precipitate delirium.[10] Cerebral metabolic failure, either by insufficient energy supply (reduced cerebral blood flow at the microcirculatory level, diminished oxygenation, relative glycopenia) or impaired energy utilization (impaired astrocyte glucose utilization), has long been reasonably suspected to play a role in the pathogenesis of ICU delirium; yet, there is scant evidence to support this theory.[11]

ETIOLOGY

The etiology of ICU delirium is multifactorial, often involving a complex interaction among various predisposing and precipitating factors. Delirium typically signifies a baseline vulnerability. Predisposing factors such as advanced age, pre-existing cognitive impairment, comorbidities, and a history of alcohol or tobacco abuse can increase a patient's susceptibility to developing delirium. Patients with extensive chronic comorbidities and reduced brain reserve may develop delirium even with a low severity of acute illness. While these factors are present upon admission and may not directly cause ICU delirium, they can make patients more prone to developing delirium when exposed to triggers such as acute illness, medications, or environmental stressors.

Precipitating factors such as mechanical ventilation, immobility, sleep disruption, urinary catheters, and multiple procedures are acquired during hospitalization. These

factors can trigger or exacerbate delirium in individuals who may already be predisposed to it. Understanding these factors and their interaction is crucial for both, the prevention and management of ICU delirium. Therefore, the individual patient's physiologic reserve and the severity of the current illness typically determine whether a patient will develop delirium during ICU hospitalization or not.

Among the numerous previously identified predisposing risk factors for delirium development, the most pertinent ones include advanced age and pre-existing cognitive dysfunction.[12–14] Indeed, more than 50% of patients who develop delirium during hospitalization have baseline cognitive impairment.[14] Additional predisposing risk factors that increase a patient's susceptibility include visual impairment, hearing loss, a history of alcohol abuse, depression, malnutrition, and baseline functional impairment.[15–17]

When assessing delirium in the ICU, it is imperative to determine the diagnosis of the acute critical illness triggering the delirium. Multiple medical conditions can be responsible for ICU delirium, including infections, metabolic derangements, autoimmune conditions, malignancies, seizures, neurodegenerative disorders, psychiatric disorders, and trauma (**Table 1**).

Furthermore, delirium may be iatrogenically caused, with polypharmacy being the most common culprit. Research indicates that the addition of three or more medications during hospitalization triples the risk of delirium.[18] While various medications can induce delirium, anticholinergic agents, opioids, benzodiazepines, and corticosteroids are most frequently implicated (see **Table 1**). Serotonin-enhancing agents and certain antibiotics (such as cefepime) can also induce delirium in susceptible patients.[19,20]

Studies specifically highlight benzodiazepines, like lorazepam and midazolam, as independent risk factors for ICU delirium, with higher doses associated with increased likelihood of occurrence.[21,22] Opioids, especially morphine, also heighten the risk of delirium, and patients receiving both opioids and benzodiazepines during their ICU stay tend to experience more prolonged delirium.[22] Delirium can also be precipitated by recreational drug use, either after intoxication or from withdrawal.

Surgical procedures have also been identified as an independent risk factor for the development of ICU delirium. Among the various surgical procedures, patients undergoing thoracic surgeries (both cardiac and non-cardiac) are particularly prone to developing ICU delirium.[23]

The ICU environment is a major sleep disruptor. Factors such as noise, constant alarms, frequent neurologic assessments, and medication administration contribute to poor sleep quality. Compromised sleep has been recognized as a risk factor for the development of delirium.[21]

CLINICAL PRESENTATION

ICU delirium can manifests in various forms, presenting a spectrum of symptoms. Critically ill patients may exhibit hypoactive, hyperactive or mixed delirium.[24]

Hypoactive delirium is characterized by reduced psychomotor activity, often resulting in patients being lethargic, withdrawn, or abulic. Conversely, hyperactive delirium manifests as agitation, combativeness, loud vocalization, aggressive behavior, hallucinations, impulsivity, and restlessness. Patients experiencing mixed hypoactive/hyperactive delirium fluctuate between the above-mentioned symptoms. In critical care settings, ICU delirium most commonly presents as hypoactive or mixed, which account for over 90% of cases. Unfortunately, hypoactive delirium is frequently overlooked and is associated with the poorest prognosis.[25]

Table 1
Causes and contributing factors of ICU delirium

Diseases	Medications	Environmental Triggers
Vascular:	Anticholinergics	Urinary catheters
• Ischemic stroke	Benzodiazepines	Restrains
• Intracranial hemorrhage	Opioids	Sleep deprivation
• Dural venous sinus thrombosis	Antihistamines	Frequent neuro checks and vital signs check
Infectious:	Antiepileptics	Constants alarms
• Meningitis/encephalitis	Muscle relaxants	Multiple procedures or surgeries
• UTI	Dopamine agonists	
• Pneumonia	Steroids	
• Intraabdominal infectious	Nonsteroidal anti-inflammatory drugs	
• Sepsis/Bacteremia	Fluoroquinolones	
• Endocarditis	Cephalosporins	
Autoimmune:	Beta blockers	
• Autoimmune encephalitis	Digitalis	
• Neuropsychiatric lupus	Lithium	
Metabolic:	Monoamine oxidase inhibitor	
• Electrolyte disarrangements		
• Hepatic encephalopathy		
• Uremic encephalopathy		
• Hypoxia		
• Hypercarbia		
• Dehydration		
• Nutritional deficiencies		
Endocrine:		
• Hypothyroidism		
• Hyperthyroidism		
• Hypoglycemia		
• Hyperglycemia		
• Hypercortisolism		
• Hypocortisolism		
Neoplasm:		
• Primary CNS tumor		
• Brain metastasis		
• Carcinomatous meningitis		
• Paraneoplastic encephalitis		
Epilepsy:		
• Seizures		
• Non-convulsive status epilepticus		
Psychiatric disorders		
Neuroleptic malignant syndrome		
Serotonin syndrome		
Other toxidromes		

DIAGNOSIS

To ensure delirium is not missed and is timely managed upon recognition, utilizing validated standardized tools for ICU delirium detection is crucial. Routine implementation of the Confusion Assessment Method for the ICU (CAM-ICU) score (Fig. 1) for every patient in the ICU, except those with a Richmond Agitation Sedation Scale score less than −3 (ie, deeply sedated) (Table 2), has been shown to reduce unrecognized cases.[26] However, systematic screening for delirium remains deficient in many ICUs. Nurses frequently find diagnosing delirium in intubated and sedated patients challenging, although the CAM-ICU score is specifically tailored for this population.

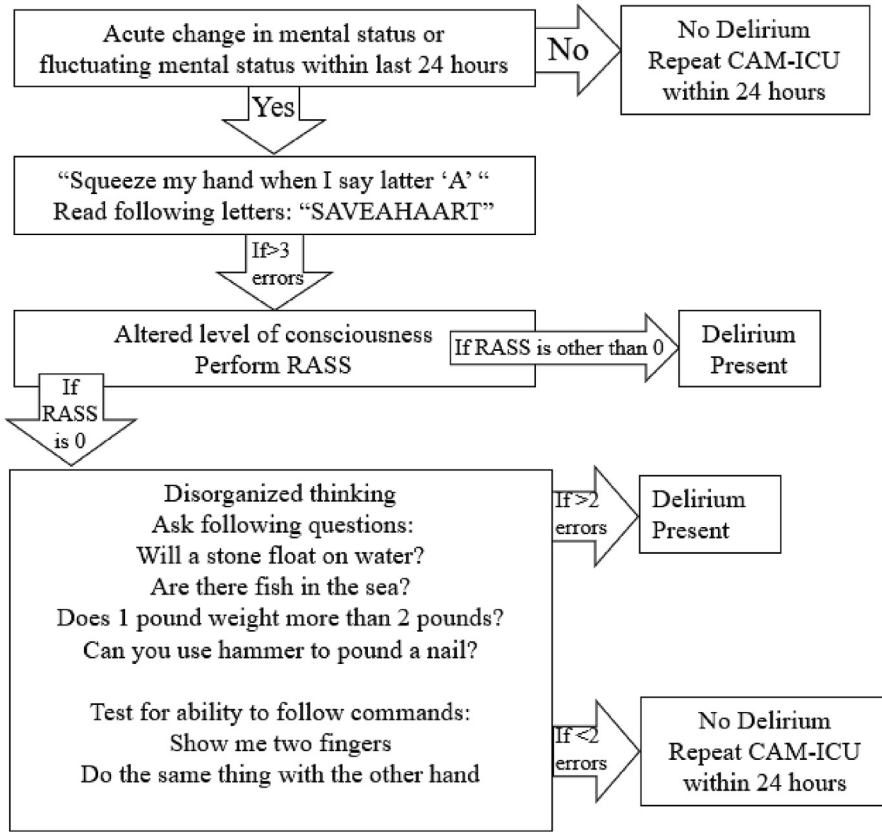
Acute change in mental status or fluctuating mental status within last 24 hours
No
No Delirium Repeat CAM-ICU within 24 hours
Yes
"Squeeze my hand when I say latter 'A' " Read following letters: "SAVEAHAART"
If>3 errors
Altered level of consciousness Perform RASS
If RASS is other than 0
Delirium Present
If RASS is 0
Disorganized thinking
Ask following questions:
Will a stone float on water?
Are there fish in the sea?
Does 1 pound weight more than 2 pounds?
Can you use hammer to pound a nail?
Test for ability to follow commands:
Show me two fingers
Do the same thing with the other hand
If >2 errors
Delirium Present
If <2 errors
No Delirium Repeat CAM-ICU within 24 hours

Fig. 1. Confusion assessment method in the ICU-CAM-ICU.

Despite concerns about its perceived time-consuming nature and complexity,[27] studies indicate that completing the CAM-ICU assessment typically takes only 2 to 5 minutes.[28] The Intensive Care Delirium Screening Checklist (ICDSC) is another useful tool for the bedside detection of delirium.[29] Unlike the CAM-ICU (a dichotomous

Table 2
Richmond agitation sedation scale for the assessment of depth of sedation

+4	Very combative, violent, dangers to staff
+3	Pulling catheters and tubes, aggressive
+2	Frequent non purposeful movements, fights ventilator
+1	Anxious but movements not aggressive or vigorous
0	Alert and calm
−1	Awakes (eye contact) for > 10 s in response to voice
−2	Awakes (eye contact) for < 10 s in response to voice
−3	Eye opening or movement to voice without eyes contact
−4	No response to voice, but eye opening or movement to physical stimulation
−5	No response to voice or physical stimulation

score), the ICDSC (an ordinal scale) can gauge delirium severity. The CAM-ICU-7 is a modification of the CAM-ICU designed to provide information on delirium severity.[30] Good correlation between the ICDSC and CAM-ICU-7 has been reported.[31]

It is well-established that without the use of standardized validated tools, delirium in the ICU often goes unnoticed, therefore, we strongly advocate for daily screening (ideally once every nursing shift) using validated tools, as missed diagnoses can lead to lack of appropriate treatment.

TREATMENT

Medical/Pharmacologic Management

Managing ICU delirium has always posed challenges due to limited pharmacologic options. Historically, haloperidol was the preferred agent, based on a small study involving 15 delirious ICU patients who underwent cardiac surgery in 1978.[32] In 2002, SCCM guidelines also recommended haloperidol for managing ICU delirium. However, this recommendation was reconsidered when subsequent studies revealed that first-generation antipsychotics increase mortality rates among elderly patients.[33]

Perspectives on antipsychotic use shifted after a randomized controlled trial involving 142 mechanically ventilated patients with delirium. Patients were randomized to receive either intravenous haloperidol or normal saline until delirium-free or discharged from the ICU. The study found no difference in delirium-free days, delirium duration, or survival between the groups.[34]

Similarly, the MIND USA trial, a randomized double-blind controlled trial comparing ziprasidone, haloperidol, and placebo, found no difference in delirium-free days or survival among patients receiving antipsychotics versus placebo. Interestingly, a randomized double-blind study among hospice patients comparing haloperidol, risperidone, and placebo found an increase in delirium symptom severity among those who received antipsychotics.[35]

These studies led to a change in SCCM guidelines, advising against the routine use of haloperidol or atypical antipsychotics for delirium treatment in critically ill patients.[36]

The use of pharmacologic agents like dexmedetomidine and ketamine remains a subject of debate. Double-blind randomized controlled trials comparing dexmedetomidine to midazolam or lorazepam revealed that patients sedated with dexmedetomidine had a 23% lower risk of delirium compared to those treated with midazolam[37] and experienced half as many delirium days compared to patients treated with lorazepam.[38] A recent Cochrane analysis suggested that dexmedetomidine may shorten delirium duration, mechanical ventilation, and ICU stay, with no reported difference in long-term cognitive impairment or mortality.[39]

Moreover, a randomized controlled trial comparing a single intraoperative dose of ketamine to placebo found no difference in delirium incidence between the groups, although patients in the ketamine group experienced a higher incidence of hallucinations and nightmares.[40]

To date, no pharmacologic agent has demonstrated a significant effect on delirium incidence, duration, or prevention. Therefore, current SCCM guidelines advise against the routine use of dexmedetomidine, ketamine, or first- or second-generation antipsychotics in delirium management.[36] However, if we need to treat agitated delirious patient to prevent injury from agitation, dexmedetomidine may be a preferred agent.

NONPHARMACOLOGICAL MANAGEMENT

Prevention strategies, such as limiting risk factors, promoting optimal sleep hygiene, employing a judicious approach to analgosedation, avoiding unnecessary invasive

procedures, facilitating early mobilization, and providing frequent reorientation, have become the cornerstone of delirium management in the ICU.

ABCDEF bundle (Fig. 2) is a validated comprehensive approach to managing critically ill patients in the ICU, with a specific focus on preventing and managing delirium.[41] Each letter in the ABCDEF bundle represents a different component of care aimed at optimizing the quality of ICU care: assessment of pain, effective delivery of analgesia and judicious use of sedation, daily spontaneous awakening trials (when appropriate coupled with spontaneous breathing trials), delirium monitoring/management, early

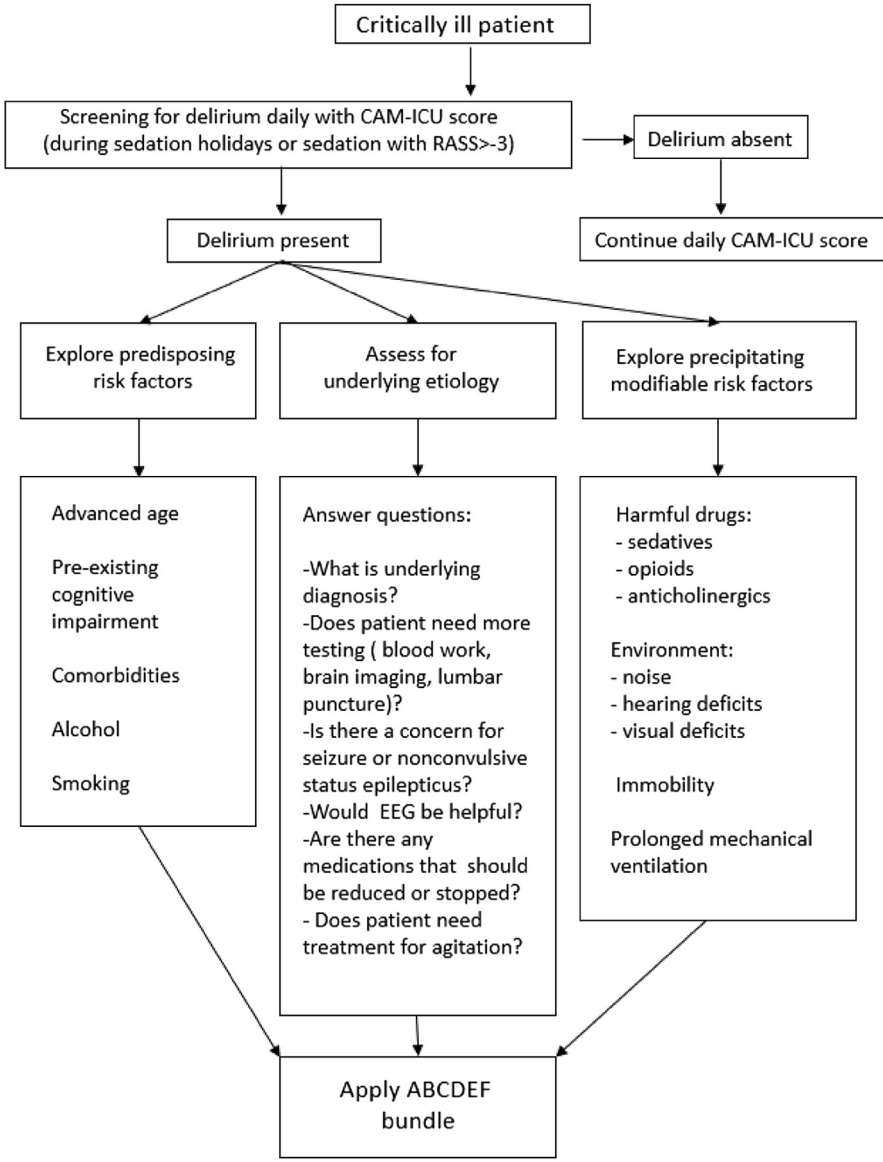

Fig. 2. Approach to ICU delirium.

exercise/mobility, and family engagement and empowerment. By addressing these six key components of care, the ABCDEF bundle may improve patient-centered outcomes, including a reduction in the incidence of delirium. Implementing the ABCDEF bundle requires a multidisciplinary team approach involving physicians, nurses, physical therapists, respiratory therapists, pharmacists, and other healthcare providers. There is evidence that compliance with the ABCDEF bundle is associated with a reduction in mortality and an increased number of delirium-free days,[42] though the beneficial impact of the bundle on the occurrence and duration of delirium has not fully consistent across different studies.[43]

PROGNOSTIC IMPLICATIONS

Delirium is associated with poor outcomes and increased mortality both during hospitalization and up to 1 year after discharge.[44,45] Patients who develop delirium within the first 24 hours of ICU admission have a higher risk of in-hospital mortality.[46] Delirious patients often require prolonged mechanical ventilation and face challenges during the weaning process.[47–49] In addition to having worse short-term outcomes, patients who experience delirium during hospitalization are at increased risk of developing dementia within the subsequent year, compared to those without delirium.[50,51]

Research indicates that over 70% of ICU survivors who experienced delirium during hospitalization exhibit cognitive impairment at 3- and 12-month follow-up, with a significant proportion experiencing moderate to severe impairment.[27,28,52] Notably, patients with pre-existing Alzheimer disease who develop delirium during ICU admission experience a worse trajectory of cognitive decline compared to those without delirium, even after accounting for disease severity and comorbidities. Neuroimaging in these patients confirms greater brain atrophy and more severe white matter disease.[53]

Delirium is often dismissed as a transient and benign condition, particularly among older patients, but this is a hazardous misconception. Delirious patients older than 65 years have a twofold increased mortality rate as compared to those who do not develop delirium during hospitalization.[51] Therefore, early recognition, prevention, and management of delirium must be a priority when caring for older critically ill patients.

The socioeconomic burden of delirium is substantial. Occurrence of delirium is associated with longer ICU and hospital stays, increased likelihood of discharge to skilled nursing facilities, and higher healthcare costs.[54–57] Delirious patients are less likely to return to work after discharge compared to those without delirium during hospitalization.[58]

Lastly, the psychological impact of delirium on ICU patients is substantial, with over 30% of survivors reporting depressive symptoms at 3-month follow-up, and 7% receiving a diagnosis of posttraumatic stress disorder (PTSD). Pre-existing diagnoses of military-associated PTSD, anxiety, and depression are associated with a higher likelihood of developing ICU-related PTSD[59,60]

SUMMARY: WHAT TO REMEMBER AT THE BEDSIDE

ICU delirium is a prevalent and severe complication of critical illness, associated with increased morbidity, prolonged mechanical ventilation, extended hospital stays, exacerbated cognitive decline, and higher mortality rates. Despite increased awareness of the problem by ICU providers, delirium still often goes undetected and underdiagnosed. It is crucial to remember that most cases of delirium are hypoactive. While hyperactive delirium is more obvious, hypoactive delirium may carry worse prognosis.

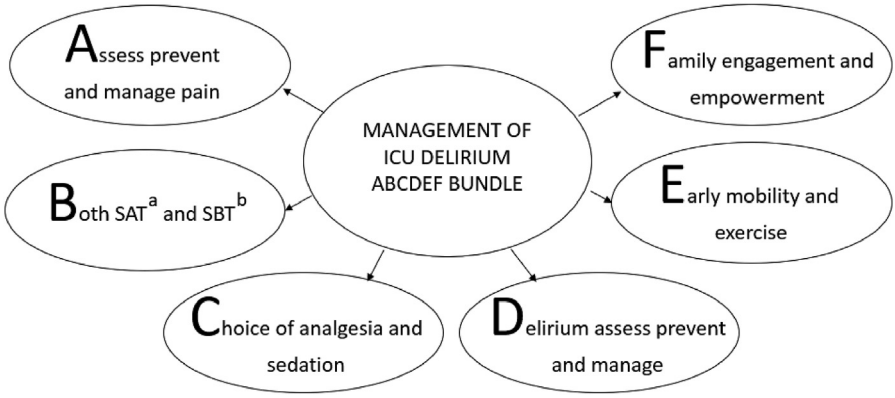
Assess prevent and manage pain
Both SAT[a] and SBT[b]
Choice of analgesia and sedation
Delirium assess prevent and manage
Family engagement and empowerment
Early mobility and exercise
MANAGEMENT OF ICU DELIRIUM ABCDEF BUNDLE

Fig. 3. ABCDEF bundle. SAT, spontaneous awakening trials; SBT, spontaneous breathing trials.

Upon detecting delirium, physicians must investigate its underlying etiology. Key questions to address include determining if the underlying diagnosis is known; whether additional testing is necessary (such as blood work, brain imaging, electroencephalography or lumbar puncture); evaluating potentially harmful medications that should be reduced or discontinued; identifying factors that could exacerbate delirium (such as removable indwelling catheters, sleep deprivation, poor mobilization, or missing hearing aids or glasses); and assessing the need for agitation treatment (see Fig. 2). Once these questions are addressed, a multidisciplinary ICU team including physicians, nurses, physical therapists and respiratory therapists should implement the ABCDEF bundle (Fig. 3). Simple non-pharmacological interventions incorporated into this bundle - such as frequent reorientation, ensuring good quality of sleep, and providing hearing aids or glasses - can be useful to reduce the burden of delirium. Minimizing sedation, particularly with benzodiazepines, may help avert or mitigate delirium. Antipsychotic medications (eg, haloperidol, quetiapine or olanzapine) should be reserved for patients with overt agitation, understanding that they do not treat the delirium per se or reduce its duration.

ICU delirium is far from benign and is linked to serious complications. Unfortunately, it is often overlooked, highlighting the need for increased attention to its detection, management, and prevention. Regular utilization of validated tools for early detection, such as the CAM-ICU score, is strongly advised. It's important for clinicians to recognize that agitation may not always be present and that hypoactive delirium, while more common, poses a greater diagnostic challenge and carries a poorer prognosis. Understanding the underlying causes is essential for effective management.

CLINICS CARE POINTS

- Think about ICU delirium in your everyday practice
- Utilize standardized and validated tools for early delirium detection
- Investigate potential causes and eliminate iatrogenic factors
- Address the underlying critical illness
- Reduce environmental factors that may exacerbate delirium

- Encourage early mobilization
- Prioritize quality of sleep
- Limit the use of sedatives, antipsychotics, and opioids whenever feasible.
- Implement the ABCDF bundle
- Engage multidisciplinary teams for comprehensive care

DISCLOSURE

Authors declare that they have no conflict of interest.

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Refractory and Super-Refractory Status Epilepticus

Therapeutic Options and Prognosis

Andrea O. Rossetti, MD*

KEYWORDS

• Treatment • General anesthetics • Ketogenic diet • Outcome • Mortality
• Continuous electroencephalogram

KEY POINTS

- The underlying biologic background represents the main prognostic variable in status epilepticus (SE). Targeting the underlying etiology, if identified, represents the best pathway to success.
- In refractory SE, general anesthetics should be used early in generalized convulsive and nonconvulsive SE in coma.
- In new-onset refractory SE/febrile-induced refractory epilepsy syndrome, immunologic treatments should be administered early after ruling out an infection.
- The pharmacologic treatment of SE after cardiac arrest should be oriented by multimodal prognostication.

INTRODUCTION

Definitions and Electreoencephalogram Diagnosis

One of the most common neurologic emergencies implying an acute risk of mortality—status epilepticus (SE)—is defined as an epileptic seizure continuing beyond 5 min (generalized convulsions) to 10 min (focal seizures), or recurring within the same timeframe without recovering the baseline clinical status.[1] SE is currently classified using a syndromic approach, including clinical signs, etiology, electroencephalogram (EEG) features, and age (see[1] for details). If an SE episode persists despite administration of at least 2 adequate antiseizure medications (ASM), including a benzodiazepine, it is labeled as refractory (RSE)[2]; if it continues despite at least 1 attempt of general anesthetics, it is called super-refractory (SRSE).[3]

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Neurol Clin 43 (2025) 15–30
https://doi.org/10.1016/j.ncl.2024.07.002 **neurologic.theclinics.com**
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New-onset refractory SE (NORSE) represents an entity arising in previously healthy patients without any obvious acute, structural, or toxic-metabolic cause. Febrile-induced refractory epilepsy syndrome (FIRES) corresponds to a subgroup occurring during a febrile illness preceding SE onset by 1 to 14 d.[4]

Critically-ill patients with reduced consciousness may have seizures and SE (mostly lacking clinical correlates: nonconvulsive SE, NCSE) in a proportion depending on the underlying condition[5–7] (**Table 1**), while up to 15% of patients with convulsive SE can have ongoing NCSE after movements wean off.[8] This highlights that EEG is indispensable for NCSE diagnosis, which by definition should last longer than 10 min or than 20% of the EEG recording,[9] with rhythmic or periodic discharges faster than 2.5 Hz, or, if not, showing a spatial-temporal evolution on EEG, subtle clinical phenomena, or response to ASM.[10] While in a critical-care setting more than 90% of seizures/SE are nonconvulsive,[11] nearly 75% of patients having abnormal movements do not seize,[12,13] clearly underscoring the importance of video-coupled EEG recordings.

The optimal duration of EEG recordings in intensive care unit (ICU) patients with suspected seizures is still debated. It has been demonstrated that up to 48 h are needed to detect 95% of ictal events,[11] but in a randomized trial testing continuous versus repeated routine EEG, survival and functional outcome at 6 mo were comparable, despite a significant higher sensitivity in detection of ictal events, rhythmic or periodic EEG patterns, and consequently more frequent treatment changes in the continuous EEG arm.[5] This finding probably reflects the major prognostic role of the underlying biologic background: epileptiform activity may represent in some instances a severity marker, rather than a modifiable causal factor.[14]

Etiologies

In high-income countries, cerebrovascular diseases, tumors, and brain trauma represent the most frequent causes in adults,[15,16] while in middle–low income settings[17] infections tend to lie on the top. Genetic conditions and disorders of metabolism should be considered in young children, while autoimmune causes[18] and paraneoplastic etiologies may explain several NORSE cases.[19] As outlined later, etiology represents one of the most important prognostic predictors.

Table 1
Frequency of seizures and status epilepticus in intensive care unit patients according to etiologies in decreasing order of magnitude[6,7]

	Seizures (SE Proportion)
Autoimmune encephalitis (especially anti NMDA-R)	75% (3/4)
Unconscious after generalized convulsive SE	50% (1/3)
Central nervous system infection	40% (1/2)
Hypoxic-ischemic encephalopathy	30% (9/10)
Intracerebral hemorrhage (acute)	25% (2/5)
Traumatic brain injury	20% (3/5)
No underlying neurologic condition	10% (1/3)
Subarachnoid hemorrhage (acute)	5% (3/5)
Ischemic stroke (acute)	3% (1/2)

Abbreviation: NMDA, N-methyl-D-aspartate.

Epidemiologic and Economical Aspects

While the annual incidence is estimated at 20 to 40/100′000,[20,21] SE occurs more frequently in pediatric patients and particularly in the elderly,[22] and around half of SE patients experience their first epileptic event as SE.[21,23] RSE represents roughly 1/3rd, and SRSE 1/20th of SE episodes.[23] Hospitalization-related costs increase in parallel with treatment refractoriness: a treatment-responding episode averages 5000 United States (US) $, while an SRSE around 40′000 US$.[24,25]

STATUS EPILEPTICUS TREATMENT

In parallel with efforts aimed at stabilizing airway and cardiovascular functions, a comprehensive laboratory work-up accompanied by brain imaging should be quickly performed: treatment directed toward the underlying cause, if identified, will have the highest change of success. In patients with NORSE/FIRES, active search of inflammatory/autoimmune conditions is strongly encouraged.[26,27] The pharmacologic SE treatment should be started as soon as possible upon diagnosis and is classically stratified into consecutive steps (**Fig. 1**). Existing guidelines and recommendations[7,27–29] essentially rely on evidence regarding early generalized convulsive SE treatment, and adherence to them may contribute preventing refractoriness.[30]

Intravenous (or Through Other Routes) Benzodiazepines: First Step

This relies on several congruent randomized controlled trials.[31–34] Midazolam 0.15 mg/kg (which can also be administered intramuscularly or intranasally), lorazepam 0.1 mg/kg, or clonazepam 0.015 mg/kg represent the most used options; it seems important to administer adequate doses to prevent refractoriness, and clonazepam appears less frequently underdosed than the other compounds.[35,36]

Intravenous Antiseizure Medications: Second Step

These compounds are often administered virtually together with the 1st step; (fos-) phenytoin (20 mg/kg), valproate (40 mg/kg), and levetiracetam (60 mg/kg) were found

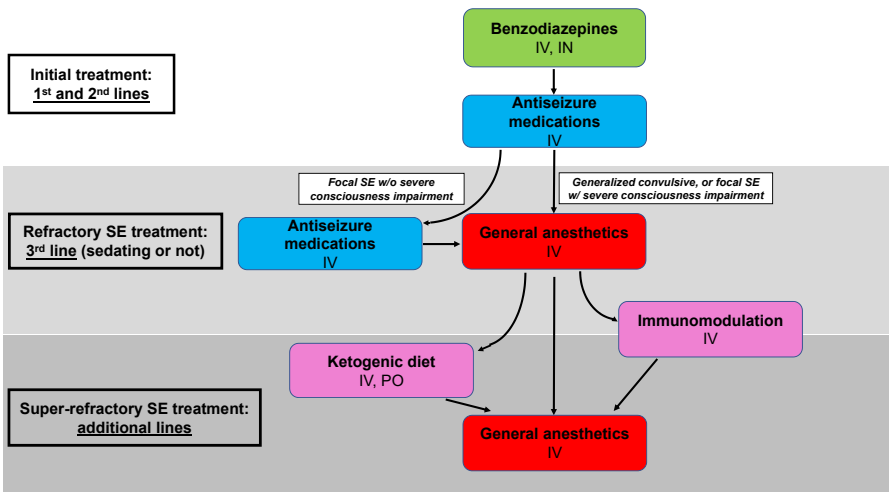

Fig. 1. Schematic workflow of the pharmacologic treatment of status epilepticus. See text for details. IN, intranasal; IV, intravenous; PO, per os (oral).

to be equivalent in a randomized trial.[37] However, valproate (enzyme inhibitor) and especially phenytoin (enzyme inducer) have several pharmacokinetic interactions. Moreover, valproate can induce an encephalopathy that may mimic ongoing NCSE.[38] Alternatives that have been studied less rigorously, but are increasingly used in practice, include lacosamide (8 mg/kg),[39,40] or brivaracetam (2 mg/kg).[41,42]

Refractory Status Epilepticus: Third Step

Refractoriness to treatment, occurring in about 1/3 of SE patients, is more likely in those with acute symptomatic forms compared to those suffering from remote etiologies or with an already known epilepsy; as stated earlier, adherence to initial treatment guidelines seem to lower this proportion.[23,30] Importantly, in a recent large multicenter observational study, while the likelihood of treatment response dropped after the first (roughly 50%) and second (roughly 20%) treatment lines, it remained somewhat stable at around 15% afterward, even after several treatment attempts.[43]

At this step, general anesthetic treatment is recommended for generalized convulsive refractory SE and NCSE in coma.[28,44] Conversely, subjects having focal SE lacking a significant consciousness impairment are relatively frequently managed outside the ICU using non-sedating ASM listed earlier.[45] Further alternatives, especially for focal RSE may be pregabaline (eg, started at 75–150 mg bid[46]), topiramate (eg, started at 50-100 mg bid[47]), or perampanel (eg, started at 8-12 mg bid[48]) administered through a nasogastric sonde. These options can, however, be difficult to implement if enteral absorption is compromised.

The routine prescription of general anesthetics for RSE is controversial, as different observational studies described an association with and increased risk of morbidity and mortality[49–51]; however, this association seems no longer significant after adjusting for SE refractoriness.[52,53] In fact, high-dosed anesthetics[54,55] and early coma induction[56,57] have been described to lead to successful SE control, albeit with some methodologic concerns.[58] It seems reasonable to interpret these data on the risk-benefit balance favoring general anesthetics in convulsive RSE, and differing them in focal RSE; admittedly, this recommendation still awaits formal confirmation.

Table 2 summarizes the most frequently used anesthetics; midazolam and propofol seem to have comparable efficacy and safety,[59] while displaying a lower risk of medical complications than barbiturates (which cumulate in the fat tissue, leading to excessive sedation and longer duration of mechanical ventilation[60,61]). The drips should be adjusted to reach seizure control, best achieved using continuous video-EEG[28,44,62]: EEG-guided therapy has been associated with a shorter duration of anesthetic treatment.[59]

The optimal EEG target remains unclear.[7] There are some reports pointing out that EEG burst-suppression or complete suppression is not associated with improved RSE control,[60,63] and deeper sedation may indeed be associated with complications and worse outcomes.[60,64,65] Seizure suppression, tolerating over time few, short-lasting seizures to limit complications associated with deep sedation, seems to represent a reasonable EEG target. Also, duration of general anesthetic treatment and weaning modalities lack any solid evidence. While sedations lasting 24 to 48 h are often recommended,[7] shorter courses at high infusion rates might prove successful.[55] It seems advisable to taper general anesthetics progressively over some hours to minimize the risk of withdrawal seizures; during this time and for 12-24 h following anesthetic interruption, ongoing EEG will allow detecting seizure recurrence. In case of SE recurrence, an anesthetic should be restarted targeting seizure control, but in this context it is useful to remind that non-epileptic rhythmic patterns (generalized periodic discharges related to anesthetic withdrawal, GRAW) might emerge during anesthetic

Table 2
General anesthetics for refractory and super-refractory status epilepticus[7,121]

	Midazolam[a]	Propofol[a]	Thiopental	Pentobarbital[b]	Ketamine[c]
Principal mechanism of action	$GABA_A$ agonist	$GABA_A$ agonist	$GABA_A$ agonist	$GABA_A$ agonist	NMDA antagonist
Half-life	2–6 h	0.5–2 (−30) h	3–22 h	15–50 h	2.5–3 h
Adverse effects	Hypotension	Hypotension PRIS Abnormal movements, shivering	Hypotension Paralytic ileus Immune depression	Hypotension Paralytic ileus Immune depression	(Cardiovascular and respiratory stimulation)
Induction bolus	0.2 mg/kg	2 mg/kg	2 mg/kg 50 mg/min	5 mg/kg 50 mg/min	2 mg/kg
Maximal infusion rate	4 mg/kg/h	5 mg/kg/h	5 mg/kg/h	5 mg/kg/h	10 mg/kg/h
Comments	Tachyphylaxis	Administer together with low dose benzodiazepine	Cumulation in fatty tissue	Cumulation in fatty tissue	Administer together with a low dose benzodiazepine

All cause hypotension.

Abbreviations: GAB_A, gamma-amino-butyric acid A; NMDA, N-methyl-D-aspartate; PRIS, propofol infusion syndrome.

[a] Midazolam and/or propofol are recommended as initial RSE treatments if general anesthetics are required.

[b] Pentobarbital is a thiopental metabolite.

[c] Ketamine is recommended for SRSE.

weaning[66,67]; these patterns often show a triphasic appearance reactive to stimuli, and do not represent recurrence of SE: they spontaneously wean after some hours, and should not trigger general anesthetics escalation.

Several complications may appear during RSE treatment, such as cardiac arrythmias, pulmonary or brain edema, infections, deep venous thrombosis, neuromuscular disorders, and others, and may be in part are the consequence of prolonged coma and immobilization.[7,68] Midazolam or propofol show a more favorable safety profile than barbiturates regarding risk of infection and hypotension, while tachyphylaxis is seen with midazolam infusions after 24 to 48 h, requiring dose escalation over time. Finally, propofol has a shorter half-life than prolonged midazolam infusions (and barbiturates), but bears a risk of propofol-infusion syndrome at drips exceeding 5 mg/kg/h for longer than 24 h[61,69]; hence, routine assessment of triglycerides, creatine-kinase and lactate are recommended.

Super Refractory Status Epilepticus: Fourth Step

SRSE may arise in about 1/6 of RSE episodes; many cases seem related to acute symptomatic or undetermined etiologies, including NORSE/FIRES.[23,57,70] Treatment options are supported by even less evidence than for RSE (**Table 3**).

A reasonable initial approach includes resuming the previous (if seizures were controlled) or another general anesthetic. Combining 2 or more compounds (eg, propofol with midazolam) and escalating the drip dose may be helpful, always under continuous EEG.[71] At this step, ketamine represents a potentially attractive option, as its mechanism of action through NMDA (glutamate) receptor antagonism counteracts one of the principal pathophysiologic pathways of sustained seizures[72,73]; its administration seems safe in observational studies, without depression of cardiac function or arterial hypotension.[74–76] Initially to be avoided in RSE due to their side-effect profile, thiopental or pentobarbital may represent valuable alternatives in SRSE.[77]

Non-sedating ASM should be continued to offer a "safe landing" upon awakening. The same compounds described earlier at the initial SE treatment steps should be considered. A practical rule of thumb foresees to avoid prescribing more than 3 or 4 concomitant ASM to prevent pharmacologic interactions (at this stage, the vast majority of patients displays a marked induction of hepatic metabolism, which can be mirrored by elevated serum gamma-GT); hence, their dosage should be guided by serum levels, also considering the risk of altered resorption, especially for those administered enterally. Alternatively, phenobarbital targeting serum levels as high as 30 to 60 mg/L can be considered during general anesthetics withdrawal.[78]

Table 3
Principal treatments options for super-refractory status epilepticus

ASM and general anesthetics	See text on initial treatment and RSE treatment; see **Table 2**
Immunomodulatory compounds	Corticosteroids IVIG, plasma exchanges, rituximab (anti CD20) Anakinra (anti IL1β receptor) Tocilizumab (anti IL6)
Non-pharmacological approaches	Ketogenic diet (also intravenous) Neurostimulation (vagal nerve, deep brain, cortical) Neurosurgical resection

Abbreviations: ASM, anti-seizure medications; CD, cluster of differentiate; IL, interleukin; IVIG, intravenous immunoglobulins.

Non-pharmacologic interventions can be tried in particularly difficult SRSE. Among a multitude of low-evidence approaches, ketogenic diet through enteral or intravenous (IV) formulations seems the most promising,[79–81] and represents the preferred treatment in patients with mitochondrial disorders (in those cases, valproate and propofol are strictly contraindicated due to the risk of fulminant hepatitis, respectively PRIS !). Further options include electrical stimulation, for example, of the vagal nerve with rapid escalation of the stimulation parameters,[82,83] or neurosurgic intervention, if a clearly delineated epileptogenic area is identified and amenable to resection without functional deficits.[84,85]

NORSE/FIRES represents a considerable proportion of SRSE; almost 1/5 of these patients will have antibody-mediated encephalitis,[19,86,87] and in many of the others autoimmune mechanisms are suspected. As soon as an infective cause has been reasonably ruled out, high-dose methylprednisolone (1 g/day over 5 days) tightly followed by IV immunoglobulins (0.4 g/kg/day for 5 days) or up to 7 plasma exchanges should be considered. Due to its specific antagonism on antibody-producing plasma cells, rituximab represents an important step for patients with a proven antibody-mediated condition.[26,27] In unexplained cases, para-infectious mechanisms leading to over-activation of the innate immune system could be at play[88,89]; hence, compounds acting on the interleukin (IL)-1 and IL-6 pathways, such as anakinra (interleukin 1β receptor antagonist) or tocilizumab (interleukin 6 antagonist) may be considered[90,91]; they also offer a relatively safe side-effect profile in terms of infectious complications as compared, for example, to cyclophosphamide.

SPECIAL SITUATION: HYPOXIC-ISCHEMIC ENCEPHALOPATHY

After cardiac arrest, up to 30% of comatose patients may display prolonged electrographic and/or clinical (mostly myoclonic) seizure activity.[92] For many years this has been considered a reliable sign of poor prognosis, but several observations pointed out that a minority of patients with post-anoxic SE may be successfully treated and awaken.

In this particular clinical setting, it is important to remind the importance of a multimodal prognostic approach, integrating clinical (brainstem reflexes, motor response to stimuli), neurophysiologic (EEG, somatosensory evoked potentials), biologic (serum neuron-specific enolase, NSE), and neuro-radiologic (ideally, MRI using diffusion-weighted imaging) variables.[92,93] The aim, as summarized on **Table 4**, is to orient early and reliably the caring team, by distinguishing between malignant (myoclonic) SE, which portends a very poor prognosis, from an early form of Lance-Adams syndrome, which is far less frequent but compatible with awakening if correctly treated.[94] To this extent, the timing of seizure activity onset and of underlying EEG background recovery are paramount: the earlier SE and myoclonus appear, and the later the background returns, the worse it will be for the patient.[95,96] EEG semiology also contributes to the distinction: high-voltage, diffuse and identically-looking epileptiform discharges on a suppressed background strongly suggest malignant forms, as opposed to lower-voltage spikes around the midline superimposed on a recognizable, reactive background.[94,97] Finally, return of brainstem reflexes (particularly, pupils and corneal), present cortical responses of median-nerve somatosensory-evoked potentials,[98] lack of markedly elevated serum NSE, and lack of diffuse diffusion-weighted MRI abnormalities[99] indicate the possibility of recovery upon treatment. A recently proposed EEG-based score (NEC2RAS, summarizing features including epileptiform discharges background amplitude and reactivity, upon their temporal evolution in the first few days) may help identifying patients with potentially favorable prognosis in these situations.[100]

Table 4
Differentiation between malignant post-anoxic status epilepticus and early Lance-Adams syndrome

	Malignant Status Epilepticus	Early Lance-Adams Syndrome
EEG background recovery	Early (within 24 h)	Late (after 36–48 h)
EEG epileptiform activity onset	Within 24–36 h, under sedation	After 36 h and sedation weaning
EEG epileptiform activity features	Diffuse, high-voltage, on suppressed background	Focal (midline) low-voltage, on preserved and reactive background
Pupillary and corneal reflexes	Can be absent	Present
Cortical somatosensory evoked potentials response (N20)	Can be absent	Present
Peak serum NSE within 72 h	May be > 60 μg/L	Should be < 60 μg/L
Brain MRI DWI	Diffuse, massive alterations	No or minimal alterations

Abbreviations: DWI, diffusion weighted imaging; NSE, serum neuron-specific enolase.

A recent randomized controlled trial showed that routine treatment with ASM and general anesthetics of repetitive, periodic, or ictal EEG discharges does not alter patients' outcome.[101] However, the study was probably underpowered to detect a clinically meaningful impact in the subcategory of potentially treatable patients as describe earlier. Awaiting further investigations, it seems reasonable to start prescribing ASM with anti-myoclonic properties, such as benzodiazepines together with valproate and levetiracetam (or brivaracetam); in treatment refractory patients showing in parallel a favorable multimodal prognostic profile, treatment escalation with perampanel (or zonisamide) through the nasogastric sonde and a propofol and/or midazolam course for up to 1 to 2 w may allow up to half of patients of this subgroup to awaken and reach a reasonably good functional outcome.[92,94,102,103]

PROGNOSIS

Prognostic studies are challenging in the context of SE, as in observational approaches it is difficult to isolate the effect of SE from that of the underlying etiology. Considering the most "robust" outcome, case-fatality does not appear to have significantly changed over the 30 y and lies at 10% to 15%.[104] This apparent counterintuitive finding may mirror the steadily increasing use of (continuous) EEG in the ICU[105] that likely lead to enhanced NCSE detection over time[21,106,107]: as these patients have often a more severe biologic background than those diagnosed on the emergency room or on the wards, their prognosis may be worse. Mortality seems to be mostly related to the underlying situation, such as increasing age with reduced biologic reserve, etiologies directly implying a short-term risk of death, and[108] medical comorbidities[109,110]; specific treatment seems conversely to play a relatively minor role by itself.[111] For example, adequate dosage of initially administered benzodiazepines seems to facilitate a timely control of the SE episode,[30,35] but not to influence its final outcome.[112] The refractoriness of SE represents a further prognostic variable, which seems heterogeneous according to its degree[113]: mortality rises progressively from 10% (treatment responsive forms), to 25% in RSE, and 40% in SRSE.[23] The currently most widely used SE prognostic scores, among many

possibilities,[114] consider age, seizure semiology, lack of previous seizures (as a surrogate of an acute brain insult) and extent of consciousness impairment,[115] or increasing age, etiology, comorbidities and EEG type[116]; these scales; however, do not prove very accurate in an ICU environment, where, again, the underlying illness severity plays a major role.[14,117]

Besides case-fatality, the risk of developing epilepsy has been described to increase by a factor 3 following SE (particularly RSE) as compared to a self-limited seizure.[118] Compared to epilepsy patients having not experienced SE (and thus controlling for the underlying etiology), those surviving an SE episode do not seem to be more impaired on neuropsychologic testing, although they tend to be less performant than controls without epilepsy.[119,120]

SUMMARY

Management of SE, one of the most common neurologic emergencies with a potential impact on morbidity and mortality, should consider that the underlying biologic background represents the main prognostic variable; hence the importance of identifying the underlying etiology. A swift application of a treatment protocol, initially including adequate doses of a benzodiazepine followed by an IV ASM, reduces the risk of RSE development. If RSE arises, it seems reasonable to readily use therapeutic coma-induction with general anesthetics in generalized convulsive and NCSE in coma, while further non-sedating ASM attempts may be warranted in patients with focal forms lacking profound consciousness impairment. Patients with SRSE should benefit from attempts with ketogenic diet and/or ketamine, and for those having NORSE/FIRES immunologic treatments should be administered early after excluding an underlying infection. Finally, the intensity of pharmacologic treatment of SE arising after cardiac arrest should always be tuned by the results of multimodal prognostication.

CLINICS CARE POINTS

- The underlying biologic background represents the main prognostic variable in SE. Targeting the underlying etiology, if identified, represents the best pathway to success.
- A swift application of a treatment protocol, including adequate doses of a benzodiazepine followed by an intravenous ASM, reduces the risk of refractoriness.
- In refractory SE, general anesthetic should be prescribed early in generalized convulsive and NCSE in coma.
- In refractory SE, additional non-sedating ASM should be prescribed before considering general anesthetics in focal forms. Most can be managed outside the ICU.
- In NORSE/FIRES immunologic treatments should be administered early after ruling out an infection.
- Super-refractory SE may be managed with ketogenic diet and ketamine.
- The pharmacologic treatment of SE after cardiac arrest should be oriented by multimodal prognostication.

DISCLOSURE

The author does not have anything to disclose.

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Prolonged Monitoring of Brain Electrical Activity in the Intensive Care Unit

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KEYWORDS

• Search terms • Electroencephalography • Intensive care unit • Seizures
• Critical care EEG • Long-term monitoring

KEY POINTS

- Electroencephalography (EEG) monitoring offers a continuous, real-time, cost-effective, and noninvasive method to assess cortical electrical activity in patients with or at risk for cerebral dysfunction.
- Continuous EEG is a powerful tool in the ICU in the diagnosis of nonconvulsive seizures, monitoring for responses to antiseizure management, neuroprognostication, and ischemia detection.
- Established criteria for initiation, discontinuation, ideal duration, and technical standards for long-term EEG monitoring in the critically ill have been outlined by Neurophysiology and Critical Care societies.

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Neurol Clin 43 (2025) 31–50
https://doi.org/10.1016/j.ncl.2024.08.001 **neurologic.theclinics.com**
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INTRODUCTION

The first electroencephalogram (*EEG*) was recorded over a century ago, and for several decades its use remained confined to the field of epilepsy, mainly applied to seizure detection, spell characterization, and diagnosis of epileptic disorders. EEG monitoring offers a continuous, real-time, cost-effective, and noninvasive method to assess cortical electrical activity in patients with or at risk for cerebral dysfunction. As such, its utility has expanded in the critically ill population beyond seizure detection and therapeutic monitoring of antiseizure medications (*ASMs*). Currently, continuous or long-term EEG monitoring (*LTM*) is a helpful tool for risk stratification of cerebral ischemia, neuroprognostication in hypoxic-ischemic brain injury (*HIBI*), and it has the potential to become an indispensable neuromonitoring tool in hospitalized patients given its practicality and temporospatial resolution.

This review paper summarizes the current evidence on the indications, interpretation, clinical applications, and challenges of the use of EEG in the intensive care unit (*ICU*) setting; the authors underscore its benefit as a bedside tool for the intensivist's decision-making based on multimodal parameters.

INDICATIONS FOR CONTINUOUS ELECTROENCEPHALOGRAM MONITORING IN THE CRITICALLY ILL

Following the increasing recognition of the value of EEG in the ICU setting, American and European societies of Critical Care and Neurophysiology established guidelines that delineate criteria for initiation, discontinuation, and ideal duration of LTM in the critically ill, as well as technical standards for monitoring.[1–4] Derived from existing guidelines, the main indications for LTM in the ICU include (1) recurrent seizures and/or status epilepticus without return to baseline, (2) patients without a definitive cause for their decreased level of consciousness or patients in whom the clinical examination findings are out of proportion (or not fully explained by) to injury burden captured on neuroimaging, and (3) patients with HIBI who do not regain consciousness and/or are undergoing temperature control management.[1,3] These clinical scenarios are often associated with nonconvulsive seizures (*NCSzs*) and nonconvulsive status epilepticus (*NCSE*). However, LTM has clinical uses beyond monitoring for NCSzs/NCSE, including guiding medical management of anesthetics for refractory status epilepticus, predicting ischemia risk in aneurysmal subarachnoid hemorrhage (*SAH*), and aiding in prognostication for survivors of cardiac arrest.[5]

ELECTROENCEPHALOGRAM INTERPRETATION

Aiming at standardizing the interpretation of patterns and facilitating multicenter research to unveil the clinical implications of EEG findings commonly encountered in the critically ill population, the American Clinical Neurophysiology Society (*ACNS*) has established the Critical Care EEG Terminology, which is now in its third official iteration.[6] This standardized nomenclature encompasses definitions for terms used to describe background features and hyperexcitable findings, including thresholds for electrographic seizures, electrographic status epilepticus (ESE), and the ictal-interictal continuum (*IIC*).

Background

The first section of the EEG report usually addresses the background and includes the most prevalent wave frequencies seen during the most stimulated/alert state, the continuity of background rhythm, as well as the presence of state changes including the

presence and how well developed is the sleep architecture. The rhythm during the most stimulated state is further characterized in terms of its organization: the anterior-posterior gradient (that is, the distribution of faster and lower voltage frequencies in anterior leads with predominance of slower and higher voltage frequences in the posterior leads when normal, or when abnormal, their reverse, or even absence) and the presence and the frequency (in Hz) of the posterior dominant rhythm (ie, the resting rhythm of the occipital cortex during the awake, relaxed state with the eyes closed). It is in this section of the report that the reactivity of the recording is usually noted, as well as the variability of the cerebral rhythms; their absence indicates more severe diffuse dysfunction. Asymmetries between the two hemispheres are carefully noted and described, in terms of amplitude, frequency (in Hz), and morphology. The background provides extremely useful clinical information pertaining to focal, multifocal, and/or diffuse dysfunction. For example, in mild encephalopathy, the posterior dominant rhythm may be slower than normal (ie, $\leq$8 Hz) or there may be excess delta activity (ie, $\leq$4 Hz waveforms) despite maximal alertness. As encephalopathy deepens, slower frequencies become more prevalent with concurrent loss of normal organization. In patients with higher degree of diffuse or multifocal brain dysfunction, there is disruption of the continuity, giving rise to a discontinuous or even burst suppressed/attenuated rhythm when the rhythm is interrupted by periods of attenuation (ie, voltages 10–20 μV) or suppression (ie, voltages <10 μV) for 10% to 49% or 50% to 99% of recording, respectively. Focal findings reflect focal dysfunction, which may or may not be related to structural abnormalities: focal slowing implies subcortical dysfunction, and attenuation of faster frequencies reflects cortical dysfunction. Background changes are helpful in the evaluation of the degree of cerebral dysfunction but they have no implication regarding the reversibility of such dysfunction, even when the background is markedly abnormal—a recording with diffuse suppression of cerebral rhythms in the setting of serum ammonia of 400 mcg/d does not imply irreversible cortical injury, and reemergence of rhythms is possible once levels return to normal.

Although the terminology offered standardized descriptors for background features, a framework for the interpretation of the degree of encephalopathy based on these abnormalities was not explicitly defined in the 2021 ACNS ICU EEG terminology. Not surprisingly, there is marked variability in the approaches to interpretation of these findings and resulting impressions for the degree of diffuse dysfunction across electroencephalographers, regardless of the level of experience, nomenclature expertise, and board certification status.[7] The Yale Adult Background EEG Grading Scale is an example of a pragmatic, 7-category scale (including normal and diffuse suppression of cerebral rhythms as extremes) that factors in the degree of slowing, organization, continuity, reactivity, and presence of state changes; however, to date, there is no universally accepted scale.[7]

Rhythmic and/or Periodic Patterns

In EEG, "rhythmic" refers to repetitive discharges with relatively uniform frequency and morphology that occurs without an interval between discharges. "Periodic" refers to repetitive discharges that occur with nearly regular intervals (ie, with <50% variation in the duration of interdischarge intervals). In other to be called a "pattern," regardless of being rhythmic or periodic, repetitive discharges must be sustained for at least six cycles, regardless of their frequency in Hz.

Rhythmic or periodic patterns are frequently encountered in ICU patients and can be associated with increased risk of seizures. In order to investigate the clinical significance of these patterns, the ACNS defined two main terms and several modifiers to

better describe and document their characteristics. *Main term 1* identifies the *localization* of the pattern, alluding to its source as a diffuse or (multi)focal process; the categories include generalized (*G*), lateralized (*L*), bilateral independent (*BI*), unilateral independent (*UI*), or multifocal (*Mf*). *Main term 2* characterizes the *type* of pattern into one of three categories: (1) periodic discharges (*PDs*), (2) rhythmic delta activity (*RDA*), and (3) spike and wave (*SW*). Many modifiers characterize the patterns further according to their morphology, prevalence, duration, frequency, and others—these are used to help in the interpretation of the burden of dysfunction and/or seizure risk based on their epileptiform appearance. For example, lateralized periodic discharges (*LPD*s) have the highest association with seizures, followed by lateralized rhythmic delta (*LRDA*); in the other extreme, generalized rhythmic delta activity (*GRDA*) is rather recognized as a marker of encephalopathy.[8] Furthermore, the frequency (in Hz) of PDs and focal rhythmic patterns is associated with a higher burden of bioenergetic mismatch, as metabolic activity increases with faster frequencies.[9] In fact, patterns greater than 2 Hz may lead to inadequate metabolic compensation and secondary brain injury.[10] The subsequent sections expand on the most commonly encountered patterns in the critically ill, namely GRDA, generalized periodic discharges (GPDs), LPDs, LRDA, and bilateral independent periodic discharges (*BIPDs*). Brief potentially ictal rhythmic discharges (or *BIRDs*)[11] are rhythmic patterns surpassing 4 Hz lasting less than 10 seconds—the minimum duration for electrographic seizures—that include fragments of previously identified electrographic seizures, or display evolution, and that are not otherwise recognized as a benign variant.[6] These fragments essentially reflect ictal fragments and, not surprisingly, have a high association with discrete evolving seizures.

Generalized periodic discharges

Common causes. *GPD*s (**Fig. 1**) have been described in many disease states including acute brain injury, systemic illness, and HIBI.[8,12,13]

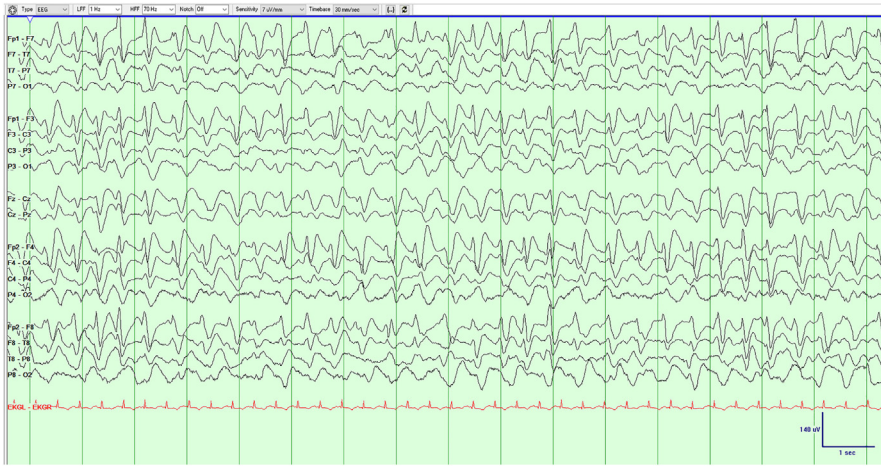

Fig. 1. Generalized periodic discharges lying on the ictal-interictal continuum. Epoch captured on longitudinal bipolar montage with high-pass filter at 1 Hz, low-pass filter at 70 Hz, paper speed of 30 mm/s, sensitivity at 7 μV/mm, and Notch filter off. A 37-year-old woman with spina bifida and neurogenic bladder, who presented with fluctuating altered mental status. EEG with frontally predominant generalized periodic discharges with associated rhythmicity, triphasic morphology, static at approximately 2 Hz meeting criteria for ictal-interictal continuum.

Clinical significance. Patients with GPDs have a higher risk for experiencing seizures (convulsive and nonconvulsive),[13] regardless of the triphasic morphology of discharges.[12] GPDs with frequencies surpassing 1.5 Hz carry a higher seizure risk, at approximately 30%, particularly if associated with plus features (eg, rhythmicity and/or ictal fast activity).[8] Furthermore, certain modifiers, such as superimposed faster frequencies, lack of triphasic morphology, anterior to posterior phase lag, and static behavior (as opposed to displaying evolution or fluctuation), have been associated, albeit inconsistently, with poorer outcomes.[12]

Lateralized periodic discharges

Common causes. LPDs (**Fig. 2**), previously termed periodic lateralized epileptiform discharges, are seen in nearly 10% of monitored patients with acute brain injury,[14] including several clinical conditions with focal lesions such as subdural hematoma, intracerebral hemorrhage, tumors, and encephalitis, of which the most classic example is herpes simplex encephalitis.[15]

Clinical significance. LPDs hold a high association with the development of seizures, with over two-thirds of patients experiencing electrographic seizures,[14] particularly when associated with plus modifiers.[8] Furthermore, patients with LPDs are five times more likely to have consciousness impairment and experience functional decline.[14]

Rhythmic delta activity

Common causes. GRDA is largely seen as a nonspecific finding in encephalopathy and not associated with a specific disease process. However, when associated with stereotypic fast activity (aka, delta brush), it carries an association with N-methyl-D-aspartate receptor encephalitis (*NMDA-R*).[16] On the other hand, LRDA, present in

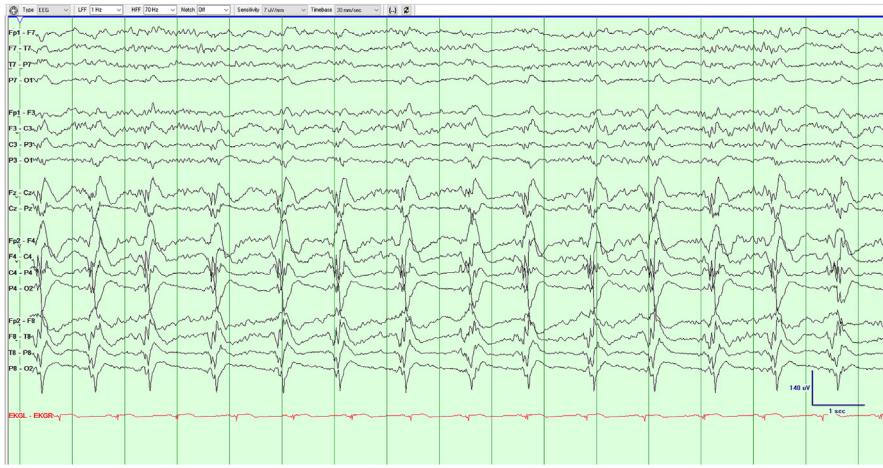

Fig. 2. Lateralized periodic discharges lying on the ictal-interictal continuum. Epoch captured on longitudinal bipolar montage with low-pass filter at 70 Hz, high-pass filter at 1 Hz, paper speed of 30 mm/s, sensitivity of 7 μV/mm, and Notch filter off. A 72-year-old woman with history of alcohol use disorder and remote epilepsy admitted with right parietal intracerebral hemorrhage and worsening encephalopathy. EEG with right hemispheric lateralized periodic discharges with associated fast activity, typically at 0.5 to 1 Hz meeting criteria for ictal-interictal continuum.

nearly 5% of critically ill monitored patients, is often seen in the setting of focal cerebral injury, such as intracranial hemorrhage.[17]

Clinical significance. LRDA (**Fig. 3**) carries a similar seizure risk to LPDs, with a further increase in the presence of plus modifiers.[8] In contrast, when the rhythmic delta activity is generalized (aka GRDA; **Fig. 4**), there is no associated increased risk of seizure, even when modifiers are present.[8]

Bilateral independent periodic discharges

Common causes. BIPDs are commonly seen in bilateral structural injury, including acute ischemic stroke, encephalitis, and HIBI.[18]

Clinical significance. The overwhelming majority of patients with BIPD have deep disorders of consciousness, and nearly half of the patients experience NCSz/NCSE. Patients with BIPD on monitoring are three times as likely to die during hospitalization and nearly seven times as likely to experience coma.[18]

ELECTROGRAPHIC SEIZURES AND ELECTROGRAPHIC STATUS EPILEPTICUS

Electrographic seizures (*ESzs*) are defined based on the Salzburg criteria as epileptiform discharges averaging greater than 2.5 Hz for at least 10 seconds or any pattern with definite evolution lasting at least 10 seconds.[19,20] *ESE* is defined according to seizure burden in minutes with the threshold of either a 10-minute continuous seizure or cumulatively, with at least 12 minutes' worth of seizures (≥20% duration) of any 60-minute period of recording meeting criteria for ESE.

ICTAL-INTERICTAL CONTINUUM

The IIC is a concept created to reflect the potential ictal clinical connotation of patterns that fail to reach the arbitrary threshold in frequency to meet the criteria for ESE and

Fig. 3. Lateralized rhythmic delta activity. Epoch captured on longitudinal bipolar montage with low-pass filter at 70 Hz, high-pass filter at 1 Hz, paper speed of 30 mm/s, sensitivity of 7 μV/mm, and Notch filter on. A 27-year-old man with cerebral palsy and epilepsy admitted with multiple breakthrough seizures. EEG with left temporally predominant lateralized rhythmic delta activity, static at 1.5 Hz and without plus features, thus not meeting criteria for ictal-interictal continuum.

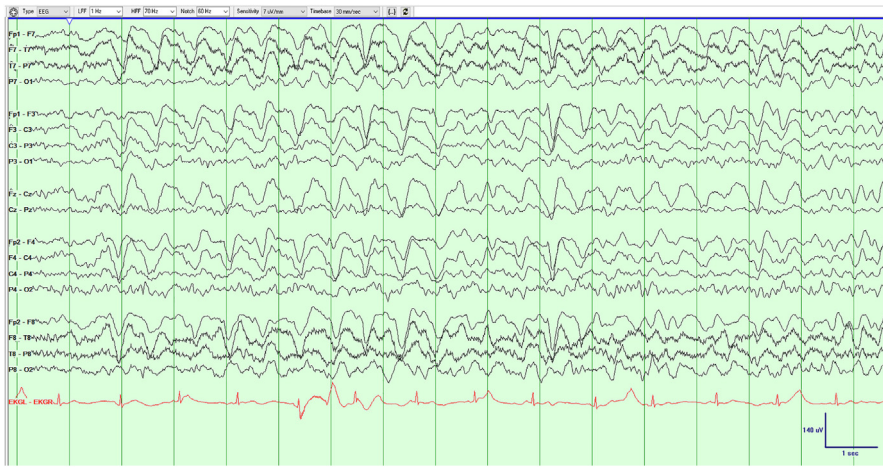

Fig. 4. Generalized rhythmic delta activity. Epoch captured on longitudinal bipolar montage with low-pass filter at 70 Hz, high-pass filter at 1 Hz, paper speed of 30 mm/s, sensitivity of 7 μV/mm, and Notch filter on. A 29-year-old woman without significant past medical history with new-onset headaches and progressive encephalopathy being evaluated for Susac syndrome. EEG with frontally predominant generalized rhythmic delta activity, with associated sharp contour, static at 1.5 Hz.

thus the possibility of these patterns reflecting *electroclinical* status epilepticus when seen in patients with altered consciousness. Akin to ESzs, IIC patterns have been associated with altered metabolism and thus may be associated with secondary brain injury.[10,21] IIC patterns are patterns that should be interpret as "possible electrographic status epilepticus" or "possible electrographic seizure," and thus warrant a therapeutic trial of parenteral ASMs.[22] If electroclinical improvement is seen, that is, improvement in EEG findings coupled with clinical improvement, the pattern is then considered ictal, reflecting definite electroclinical status epilepticus. Thus, it is not a diagnosis, but only a descriptive EEG term, and its significance must be interpreted considering the clinical context. Although widely recognized by electroencephalographers based on their subjective interpretation of the potential ictal connotation of rhythmic and/or periodic patterns, the IIC was only recently objectively defined by ACNS as patterns lasting at least 10 seconds and[6] (1) any PD or SW pattern averaging more than 1.0 Hz but less than 2.5 Hz, or (2) any PD or SW pattern with a plus modifier or fluctuation averaging more than 0.5 Hz but less than 1 Hz, or (3) any LRDA with a plus modifier or fluctuation averaging more than 1 Hz but less than 2.5 Hz, and (4) does not qualify as an ESz or ESE (see **Figs. 1** and **2** display patterns that lie on the IIC).

There are no widely acceptable approaches to the therapeutic trial for IIC. In patients with impaired alertness or at high risk of respiratory depression, a trial is recommended with a nonbenzodiazepine (to facilitate the identification of clinical improvement), parenteral ASMs at two-thirds to three-quarters of the recommended full loading dose for definite status epilepticus, or small incremental bolus doses of benzodiazepines followed by EEG monitoring for at least 15 minutes. A clinical positive response has been recently defined as a one-step improvement in their response scale or a time-locked improvement in a focal deficit. An EEG-positive response has also been defined by the resolution of the IIC pattern for at least three times the longest previously observed spontaneous interval of resolution and for at least one continuous minute.[22]

CLINICAL USES OF CONTINUOUS ELECTROENCEPHALOGRAM IN THE INTENSIVE CARE UNIT SETTING

Status Epilepticus and Seizures

Seizures are common in the critically ill and are, most commonly, nonconvulsive in nature. Thus, any patient with persistent and unexplained altered mental status in the setting of any acute brain injury should be monitored on EEG.[3] LTM should also be initiated as soon as possible in critically ill adults and children with altered consciousness following generalized convulsive status epilepticus or clinically evident seizures to rule out NCSzs and NCSE.[1,23] Patients with refractory status epilepticus—persistent seizures despite first- and second-line agents—should also be monitored on LTM to guide further therapeutic decisions.[24–26]

The 2HELPS2B score was developed and validated in a multicenter retrospective cohort to provide risk stratification for further seizures and guide duration of monitoring (**Table 1**). The score, arising from a machine learning algorithm, assigns points to EEG findings from the first hour of recording.[27,28] Those in the low-risk category (ie, score = 0) have less than 5% seizure risk and could be monitored clinically. Those in the medium risk category (ie, score = 1) have an overall 12% seizure risk and therefore warrant at least 12 hours of monitoring. Lastly, the high-risk category (ie, score >2) had a seizure risk of approximately 27% and warrant at least 24 hours of monitoring.[27] Many centers currently use the 2HELPS2B score to determine the duration of LTM on a case-by-case basis.

However, LTM is not available in many centers, and an alternative approach is to repeat short-term recordings.[29–32] In fact, the Continuous EEG Randomized Trial in Adults (CERTA) pragmatically demonstrated lack of benefit on mortality with the use of LTM compared with repeat 30-minute recordings in a multicenter cohort of 364 critically ill patients with altered consciousness. Nonetheless, LTM was associated with increased sensitivity for the detection of seizures and hyperexcitable patterns, which led to change in management with more ASM adjustments.[33]

TRAUMATIC BRAIN INJURY

Posttraumatic seizures, in their majority nonconvulsive, occur in 22% to 33% of critically ill patients with traumatic brain injury.[34–36] Posttraumatic seizures are associated with intracranial hypertension, increased cerebral metabolic distress, long-term hippocampal atrophy,[34,37] and poorer outcomes.[38]

Table 1
2HELPS2B score

Variable	Score (If Present)
Brief potentially ictal rhythmic discharges (BIRDs)	+2
LPD, LRDA, BIPDs	+1
Any history of prior seizure	+1
Sporadic epileptiform discharges	+1
Frequencies $\geq$ 2 Hz	+1
Plus modifiers	+1

Scores are associated with seizure risk and reflect the yield of continued monitoring, thus guiding duration of LTM based on an individualized seizure risk stratification.

Adapted from Struck, A.F., et al., Association of an Electroencephalography-Based Risk Score With Seizure Probability in Hospitalized Patients. JAMA Neurol, 2017. 74(12): p. 1419-1424.

Advances in quantitative EEG (*qEEG*) analysis and the use of machine learning have the potential for revolutionizing the field facilitating neuroprognostication and post-traumatic epilepsy forecasting.[39–43]

SUBARACHNOID HEMORRHAGE

NCSzs have been reported in up to one-third of patients with SAH.[44] Patients at higher risk include those who are older, have a poor clinical grade, have a large intraparenchymal hemorrhage/cisternal blood, those with ruptured anterior circulation aneurysms, and those who develop delayed cerebral ischemia (DCI).[45–47] Furthermore, nearly one in four patients with SAH has PDs, most often LPDs[48]; epileptiform activity in this context may also reflect ischemia.

Beyond monitoring for seizures, EEG has also been useful for DCI prediction. In fact, the presence of slower frequencies may predict DCI up to 2 days before it becomes apparent in other diagnostic tools.[49–53] However, less than one-third of neurophysiologists working in an ICU setting use qEEG routinely for ischemia monitoring in patients with SAH.[54] Traditional markers used to predict DCI include trends over time of decreased power of alpha frequency band, relative alpha variability, and reduced alpha/delta ratio.[55–57] These studies have shown that persistent alpha power reduction (*APR*) by more than 40% for longer than 5 hours can predict DCI, preceding transcranial Doppler detection by a mean of 1 to 2.3 days. Furthermore, those without APR on EEG were shown to have good functional outcome after 6 months.[58] At present, the use of qEEG to detect vasospasm/DCI and guide therapeutic management remains institution-specific due to lack of high-quality evidence guiding standardized use in this context.

INTRACEREBRAL HEMORRHAGE

Up to one-third of patients with intraparenchymal hemorrhage experience NCSz during index hospitalization.[59,60] Patients at higher risk for delayed seizures following hemorrhage can be identified using a risk assessment. The CAVE score consists of a 4-point score system: cortical involvement, patient's age less than 65 years, hemorrhagic volume greater than 10 cc, and early seizures. In a retrospective study, those with a CAVE score of 4 had a 46.2% risk of seizures 7 days following initial injury, suggesting the use of EEG monitoring well into injury course.[61] Furthermore, nearly one in five patients will have PD on EEG, mostly LPDs.[60]

ISCHEMIC STROKE

Patients with acute ischemic stroke have a lower incidence of seizures following initial injury compared with patients with hemorrhagic strokes, at around 10%.[59,62] However, more than one-third of patients with ischemic stroke are found to have hyperexcitable findings, particularly in the setting of cortical involvement.[63] LTM findings lead to change in ASM management in more than one in every five patients; however, neither the presence of epileptiform abnormalities nor the presence of seizures was associated with in-hospital mortality or functional outcomes in one study.[63]

Certain qEEG indices, such as the delta-theta to alpha-beta ratio and alpha relative power, accurately predict outcome following acute ischemic stroke—a finding that may even perform better than neuroimaging scores of stroke burden such as ASPECTS score in predicting outcomes.[64]

CARDIAC ARREST

The prevalence of seizures in HIBI ranges from 10% to 30%, which are mostly NCSzs[65,66] and may occur at any time during the postcardiac arrest period.[67] Prolonged monitoring in HIBI is thus essential for diagnosing NCSz/NCSE,[68] where temperature control remains a widely used neuroprotective therapy, which usually leads to confounding of neurologic examination due to need for sedation, limiting the ability to detect subtle clinical manifestations of seizures. Seizures and status epilepticus in the context of cardiac arrest are nearly universally associated with poor prognosis[69]; however, its delayed emergence in patients with preserved background continuity and lack of other predictors of poor outcomes can help identify patients with higher neurologic recovery potential.[70] The NEC2RAS EEG prognostic score (**Table 2**) still lacks validation in external cohorts but holds promise in identifying cardiac arrest patients with epileptiform findings on EEG who have a high chance for recovering consciousness.[71]

LTM in HIBI plays a key role in teasing apart cortical myoclonus—aka myoclonic seizures—from peripheral or subcortical myoclonus, as these are indistinguishable by clinical features alone.[65,66,72,73] Furthermore, different electroclinical patterns for postanoxic myoclonus, even within the spectrum of cortical myoclonus, reflect distinct recovery potential and trajectories. Elmer type 1 electroclinical phenotype with highly epileptiform bursts in lockstep with myoclonus in a suppressed background is associated with nearly universal mortality, whereas Elmer type 2 with spiky GPDs embedded in a continuous background is associated with greater chances of survival and possible recovery of functional independence.[74]

In fact, EEG is one of the most commonly used neurophysiologic neuroprognostic tools in HIBI. Several studies have examined predictors of good and poor outcome using EEG in cardiac arrest survivors.[69,75,76] Identical bursts (**Fig. 5**A), a type of burst suppression pattern first described in HIBI population, are bursts that are identical in the first 500 ms across all leads, regardless of the amplitude or subsequent duration of burst or interburst intervals; this finding is highly predictive of poor outcomes, although false-positive cases have been reported in the literature.[69] Previously the most commonly used EEG predictor of poor outcome and recommended by outdated neuroprognostication guidelines, unreactive EEG is now recognized as an unreliable predictor[69] likely due to inconsistent practices for testing and interpretation. Although international consensus exist on technical standards for EEG

Table 2
NEC2RAS score

EEG Timing from Cardiac Arrest (h)	Variable		Score (If Present)
12–36	No epileptiform	NE	+1
12–36	Continuity ≥50%	C	+1
12–36 36–72	Reactivity Reactivity	2R	+1 for each time point
36–72	Normal amplitude of background	A	+1
36–72	SIRPIDs	S	+1

Abbreviation: SIRPIDs, stimulus-induced rhythmic periodic or ictal discharges.

Scores range from 0 (worse outcomes) to 6 (best outcomes) with a prediction performance of AUC for ROC curve of 0.9734 for scores ≥4 predicting consciousness recovery.

Adapted from Barbella, G., et al., Prediction of regaining consciousness despite an early epileptiform EEG after cardiac arrest. Neurology, 2020. 94(16): p. e1675-e1683.

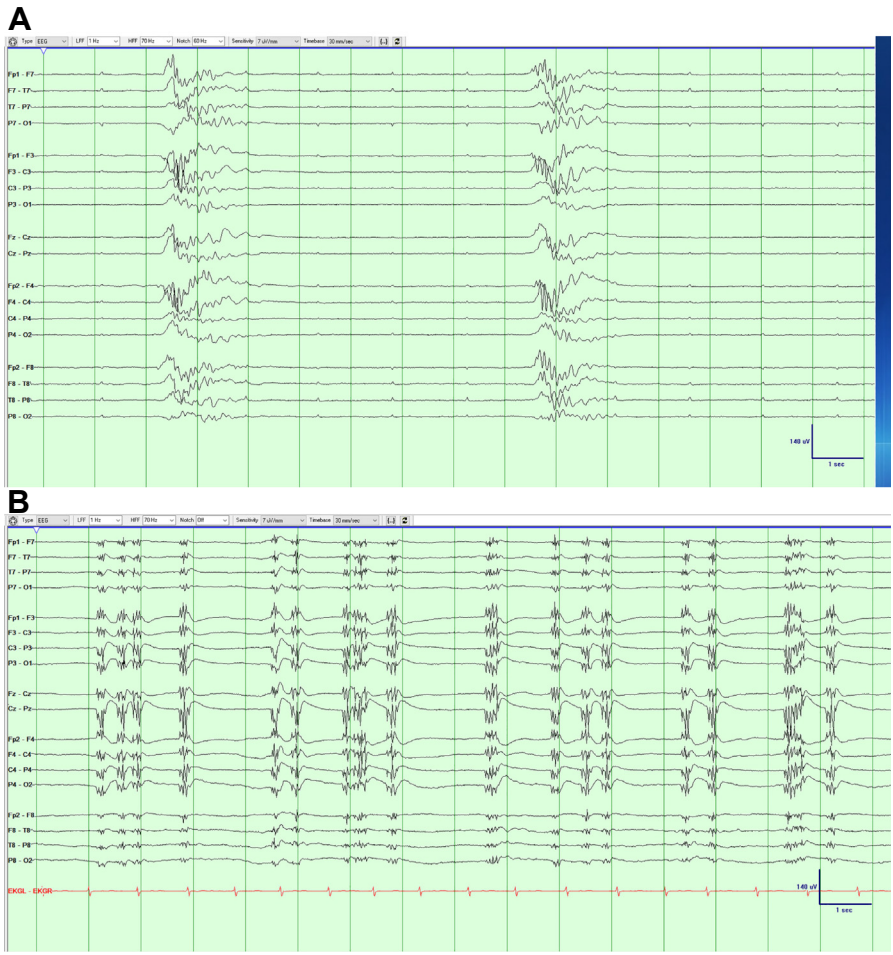

Fig. 5. Highly malignant EEG in cardiac arrest. Both epochs are captured on longitudinal bipolar montage with low-pass filter at 70 Hz, high-pass filter at 1 Hz, paper speed of 30 mm/s, sensitivity of 7 μV/mm, and Notch filter on. (*A*) A 32-year-old man with coronary artery disease who suffered a witnessed prolonged cardiac arrest. EEG displaying burst suppression pattern with highly epileptiform identical bursts. (*B*) A 86-year-old man admitted with acute symptomatic anemia from gastrointestinal hemorrhage and suffered a cardiac arrest during endoscopy. EEG displaying highly epileptiform periodic bursts (≥4 phases and lasting ≥500 ms on average, but at times only meeting criteria for polyspike discharges instead of bursts when lasting <500 ms) in an otherwise suppressed background.

reactivity testing,[77] data on their implementation by institutions and the reappraisal of reactivity as a prognostic tool when following these recommendations are lacking.

The Westhall classification set forth in 2014 proposed the stratification of EEG findings based on their hypothesized predicted value for a poor outcome in HIBI: highly malignant findings with near-zero false-positive rates (*FPRs*), malignant with <5% FPR, and benign (when none of malignant or highly malignant findings were present).[78] In a systematic review, only diffuse suppression, persistent burst suppression (**Fig. 5**A, B), and GPDs in a suppressed background—all considered highly malignant in the

Westhall classification—had very low FPR particularly within the first 24 hours from cardiac arrest, albeit none of these findings consistently sustained zero FPR across all studies.[69] Preserved continuity and reactivity have a good specificity for good outcomes but very low sensitivities (**Fig. 6**A, B).[76]

Most importantly, the EEG recording in the setting of HIBI evolves over time,[79] at times improving, which reflects cerebral resilience to insults, and other times deteriorating toward highly malignant patterns, which suggest accrual of secondary brain injury—it is of major importance to stay attuned to the evolution of clinical courses and always use EEG findings in the context of multimodal neuroprognostication.[80]

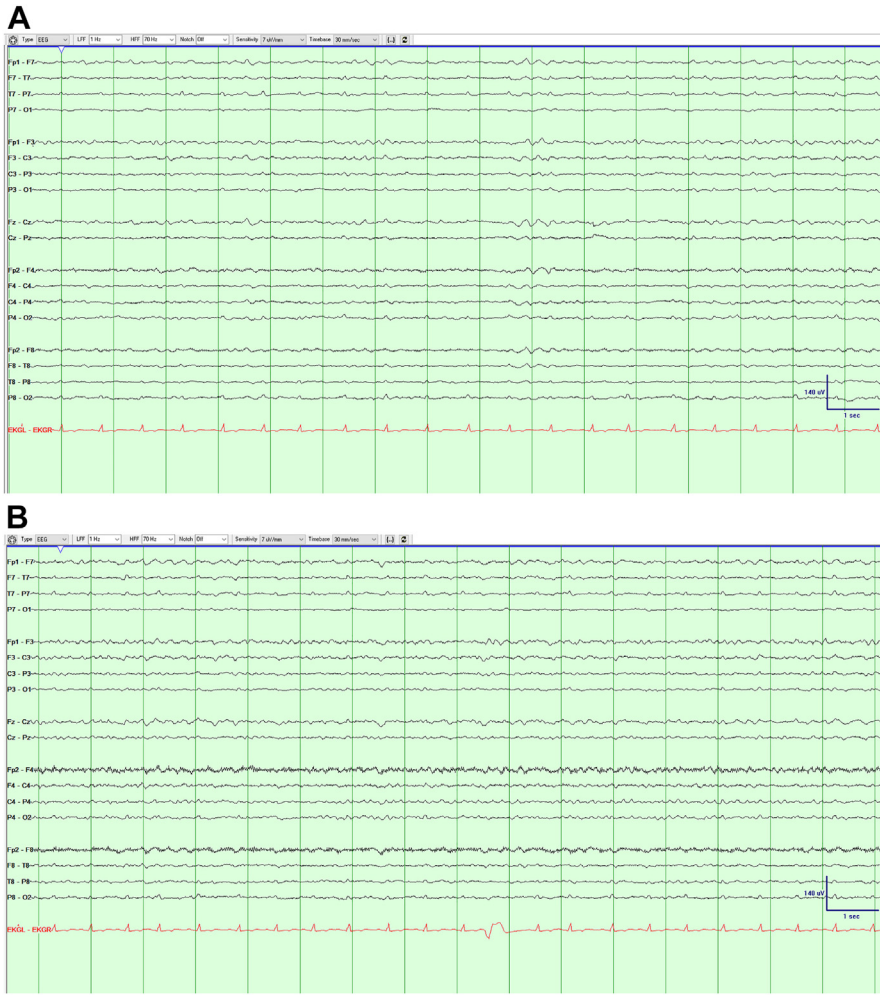

Fig. 6. Cardiac arrest EEG with good prognostic features. Both epochs are captured on longitudinal bipolar montage with low-pass filter at 70 Hz, high-pass filter at 1 Hz, paper speed of 30 mm/s, sensitivity of 7 μV/mm, and Notch filter off. A 65-year-old man with cardiac comorbidities who choked while eating at home and developed cardiac arrest with initial rhythm of ventricular fibrillation. (*A*) EEG capturing quiet state, with background mainly consisting of delta and 4 to 6 Hz theta and (*B*) EEG capturing reactivity in the most stimulated state with increased power of 6 to 8 Hz theta frequencies. Both epochs demonstrate intact continuity.

CENTRAL NERVOUS SYSTEM INFLAMMATION

The prevalence of seizures in patients with central nervous system infections ranges from 6% to 12%, often nonconvulsive, with a higher mortality associated with greater seizure burden.[81,82] Timing of occurrence is highly variable, and patients with coma often have electrographic seizures beyond the 24 hours from admission, arguing for use of prolonged continuous EEG monitoring.[83] Temporal LPDs are widely recognized as the electrophysiologic hallmark of herpes simplex virus 1 encephalitis. EEG findings are a diagnostic criteria for limbic encephalitis syndromes, with temporal sharp waves or temporal intermittent RDA seen in autoimmune encephalitis with Hu, Ma1, LGI2, and GAD antibodies[84] and "extreme delta brush" commonly seen in NMDA-R encephalitis.[16]

ACUTE ENCEPHALOPATHY IN SYSTEMIC CRITICAL ILLNESS

At the time of the ESICM guidelines release, very limited data were available on continuous EEG monitoring for patients with altered consciousness without an acute brain condition, but the same rationale for monitoring applies also to this setting.[3] Septic patients may have a wide range of encephalopathy, and likewise, range of dysfunction on EEG; approximately 10% display discharges with triphasic morphology[85] and more than 1 in 10 have NCSz.[86] Septic patients with a predominantly delta background and those with PDs are more than three times as likely to succumb during their ICU stay.[87] Other wide range of systemic derangements, including uremia and hyperammonemia, are associated with corresponding markers of cerebral dysfunction on EEG; no specific finding can be considered pathognomonic to particular causes or infallible in predicting the recovery course.

LOGISTICAL CHALLENGES

The EEG tracing of critically ill patients can be influenced by several external elements, such as lead placement variability due to skull abnormalities and the presence of artifacts caused by interference with other electronic devices in the ICU. Malfunctioning equipment may also affect the quality of the study. It is important to maintain standards for acquisition machines, including amplifiers, analog-to-digital converters, central processing units, software and monitors, and proper grounding, both for patient safety and to reduce artifacts as much as possible. Concurrent synchronized video recording is recommended to correlate the EEG tracing with clinical behavior and properly differentiate true epileptiform findings from artifactual abnormalities.[88]

In addition, many patients in the ICU require repeated neuroimaging studies, making it paramount to have computed tomography and/or MRI compatible electrodes to avoid excessive reapplication of EEG leads as well as to prevent patient harm from the use of noncompatible electrodes or skin breakdown.[89,90]

EXPANDING ACCESS TO MONITORING

Limited availability of EEG machines, technologists, and electroencephalographers pose a frequent challenge when there is an expectation to provide full-time LTM coverage and updated interpretation in a timely fashion.[91] In order to address delays in EEG monitoring, limited montage EEG, without the need for immediately present neurodiagnostic staff, has been proposed with varying degrees of success.[92,93]

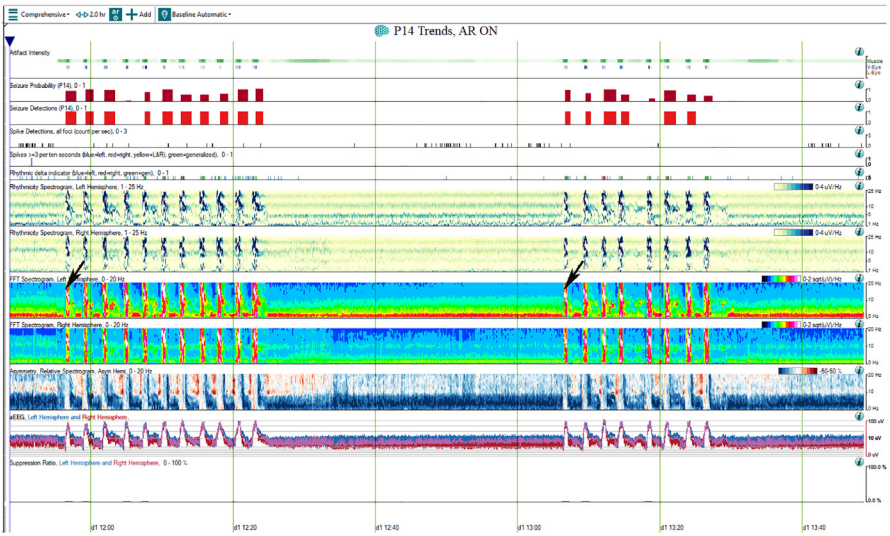
P14 Trends, AR ON
Artifact Intensity
Seizure Probability (P14), 0 - 1
Seizure Detections (P14), 0 - 1
Spike Detections, all foci (count per sec), 0 - 3
Rhythmicity Spectrogram, Left Hemisphere, 1 - 25 Hz
Rhythmicity Spectrogram, Right Hemisphere, 1 - 25 Hz
FFT Spectrogram, Left Hemisphere, 0 - 20 Hz
FFT Spectrogram, Right Hemisphere, 0 - 20 Hz
Asymmetry, Relative Spectrogram, Asym Hemi, 0 - 20 Hz
aEEG, Left Hemisphere and Right Hemisphere
Suppression Ratio, Left Hemisphere and Right Hemisphere, 0 - 100 %
d1 12:00
d1 12:20
d1 12:40
d1 13:00
d1 13:20
d1 13:40

Fig. 7. Cyclic seizures. Epoch capturing quantitative EEG trends over approximately 2.5 hours in 20-minute blocks identified by vertical green lines. A 67-year-old man with history of cerebral palsy and medically refractory epilepsy admitted with multiple breakthrough seizures. Raw EEG (not shown) revealed abundant discrete evolving electroclinical seizures characterized by onset of fast activity arising from left frontal region, gradually increasing in amplitude and diffusely spreading to the right. The qEEG displays the classic flame appearance of seizures in multiple trends (rhythmicity spectrogram, fast Fourier transform trend highlighted with *black arrows*, asymmetry spectrogram, and amplitude EEG band); seizures are occurring in nearly regular intervals meeting criteria for cyclic seizures.

A WORD ON QUANTITATIVE ELECTROENCEPHALOGRAM

As the screening of a 24-hour EEG study can take a minimum of 20 minutes and often significantly longer for a more in-depth evaluation, timely interpretation of these studies can be a significant challenge.[94] This review of raw EEG also requires specialized staff, such as a clinical neurophysiologist or epileptologist, that is not typically part of the bedside team, making real-time evaluation difficult.[94]

Quantitative EEG is the mathematical analysis of raw EEG data. Specific algorithms of quantitative EEG are called "trends," and certain commercial software, such as Persyst, can display the results as a graphical representation. These trends can be displayed over a certain epoch of time, allowing for a faster review of the EEG, highlighting significant changes such as those arising from seizures. A characteristic "flame" or "arch" on the fast Fourier transform spectrogram trend is typical of seizures (**Fig. 7**).[95] Quantitative EEG can also reveal subtle changes in the data over longer periods of time. It has also been used successfully by nonneurophysiologists in the ICU, with a sensitivity of at least 80% for detecting seizures.[96]

SUMMARY

Continuous EEG is a noninvasive method to assess cerebral function in real time, and its use has become gradually more widespread. The adherence to recommended technical standards and the standardized ICU EEG terminology used in reporting and interpretation of the recordings has led to improve understanding of clinical

implications of findings and expanded the clinical application of LTM in the critically ill. Continuous EEG monitoring can be used as a window into the brain and is an invaluable tool for the well-informed intensivist.

CLINICS CARE POINTS

- LTM should be highly considered in critically ill patients with fluctuating mental status or for whom monitoring of brain function may guide further care.
- The ideal runtime of LTM hinges on specific clinical scenarios.
- The 2HELPS2B score can be used to estimate the optimal duration for monitoring on a case-by-case basis.
- LTM provides invaluable information regarding prognostication after cardiac arrest and is indispensable for the identification of myoclonic seizures.
- Quantitative EEG is the mathematical processing of EEG, which can be displayed in graphical form and is a useful representation of change in cerebral activity over time and can be a key neuromonitoring tool in cerebral ischemia detection.

DISCLOSURE

The authors have nothing to disclose.

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Neuroworsening in Moderate Traumatic Brain Injury

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KEYWORDS

• Traumatic brain injury • Outcome • Neuroworsening • Intensive care unit

KEY POINTS

- Neuroworsening (NW) is a potentially lethal complication of moderate traumatic brain injury (MoTBI).
- The causes and risk factors of NW should be promptly identified.
- Intensive care unit should be considered whenever there are risk factors of NW.
- NW requires prompt and aggressive therapeutic approach.
- Outcome is deeply affected by NW.

INTRODUCTION

Traumatic brain injury (TBI) is still a leading cause of mortality and disability worldwide.[1,2] Despite its high prevalence, little attention has been paid to the management of moderate TBI (MoTBI), as the majority of evidence has been focused on more severe cases. The relatively limited information available explains the lack of specific guidelines.[3]

Patients with MoTBI represent 20% of all TBI admissions to the emergency department.[3,4] According to current literature, these patients are poorly defined and categorized, and there are still many unanswered questions regarding their management; in fact, MoTBI falls into a "gray area,"[3] where monitoring, neuroimaging, and therapeutic strategies are not well established.

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Neurol Clin 43 (2025) 51–63
https://doi.org/10.1016/j.ncl.2024.08.002 **neurologic.theclinics.com**
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Classically, patients with Glasgow Coma Scale (GCS) score ranging from 9 to 12 points postresuscitation are categorized as "moderate."[2] However, a recent consensus[4] recommended—based on available evidence—to include a score of 13 points of GCS in the moderate group.[5–7]

The epidemiologic profile of MoTBI may change according to age and available resources.[8] In low-income countries, for instance, MoTBI is mainly observed in young people following traffic accidents or violence and is frequently accompanied by extracranial injuries; meanwhile, in high-income countries, MoTBI is mainly observed in the elderly population (who have more comorbidities and are often taking multiple pharmacologic agents, including anticoagulants) and, in general, caused by purely cranial trauma due to low-energy impacts.[8]

TBI is a dynamic and heterogeneous entity.[1,2] Cases classified as "moderate" do not escape this assertion and can show a wide variety of clinical pictures and lesional spectrum.[3] Yet, a simple way to remember the presentation and evolution of patients with MoTBI is that about 30% will present intracranial injuries, 30% will require a surgical procedure, and 30% will present a clinical deterioration (rule of 30).[3]

MoTBI is a serious entity.[3] More than half of the individuals who suffered MoTBI will present long-term neurocognitive sequelae, many of which will be permanent and will prevent social reintegration or resumption of life prior to the trauma.[3] Furthermore, the mortality of MoTBI is not negligible, averaging around 15%.[3]

Neuroworsening (NW) is a feared complication after MoTBI.[4,9,10] NW can manifest in various ways[4,9] and may occur in different evaluative periods after trauma.[9] Multiple predisposing factors for NW have been described; however, so far, there is no validated predictive model[4,9] to guide clinicians in the early detection of patients at risk. This is a crucial point, as NW is associated with poor prognosis.[4,9,10]

Therefore, NW is a medical-surgical emergency that requires the adoption of specific protocols for its prevention, prompt detection, and aggressive management.[4,9]

NEUROWORSENING: WHAT ARE WE TALKING ABOUT?

Deterioration of neurologic status, neurologic decline, neurodeterioration, and NW are generally considered synonyms. There is currently no widely and universally validated definition for the term "NW" in MoTBI and the existing ones have been extrapolated from the severe TBI population.[4,9,11] There are different ways to define NW.[4]

Clinical Neuroworsening

Classically, NW has been described on a clinical basis as a decline in neurologic examination.

The first definitions of NW were developed as outcome measures in pharmacologic trials that included patients with moderate and severe TBI.[11,12] The criteria necessary for its definition were mainly objective (decreased of 2 or more points in the motor component of GCS (mGCS), loss of pupillary reactivity or new pupillary asymmetry [2 mm or greater]), although some others were subjective and often unclear, such as "*any deterioration in neurologic status.*"[11,12]

A New Zealand study employed a similar definition of NW after MoTBI, but the authors considered a decrease in total GCS punctuation rather than the motor component.[13] More recently, the Best Trip trial, which used a clinical and imaging protocol to manage intracranial hypertension in severe TBI, utilized the following criteria for NW[14]: (1) decrease in the mGCS greater than 2 points; (2) a new loss of pupillary reactivity; (3) interval development of pupillary asymmetry greater than 2 mm; (4) new focal motor deficit, and (5) herniation syndrome. Subsequently, consensus revised ice (CREVICE)

protocol[15] and the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC)[16] consensus defined NW in a similar manner with the exception of changing the decrease in mGCS to greater than 1 point and/or the presence of seizures. Observational studies on MoTBI have used this same definition.[17–20] Recently, the Latin American consensus on MoTBI suggested to add worsening headaches and increased intensity and frequency of vomiting to the clinical criteria to define NW in individuals who are not sedated or intubated.[4]

When analyzing the clinical criteria, it is important to consider limitations due to the need of using sedation, analgesia, and neuromuscular blockade, which can preclude examination or mask the clinical picture.

Radiological Neuroworsening

Neuroimaging, especially computed tomographic (CT) scan, is an essential tool in the management of MoTBI. In the context of MoTBI, CT scan allows the assessment of the type and extension of the lesion, its location and need for neurosurgical interventions.[21–23] Additionally, it provides important pathophysiological and prognostic information, playing an important role in the follow-up and in therapeutic decision-making.[21]

In the early 1990s, Marshall and colleagues[24] developed a tomographic scale based mainly on the presence and volume of the space-occupying lesion, the basal cisterns status, and the presence of midline shift. Additionally, this scale takes in consideration whether the hemorrhagic collections have been surgically evacuated or not.[24]

The Marshall scale has been widely validated in neurotrauma units around the world due to its predictive capacity to establish intracranial hypertension and the final outcome,[25–28] and its use has been widely extended from a research field to daily clinical practice.[25] When estimating prognosis, the controversy still persists as to whether it is optimal to use the CT on admission or the one considered “worst” in subsequent follow-up.[29]

Subsequently Maas and colleagues[30] in Rotterdam developed a predictive model based on CT scan parameters obtained from logistic regression analysis, which included basal cisterns status, midline shift, and the presence or absence of intraventricular bleeding (intraventricular hemorrhage [IVH]), subarachnoid hemorrhage (SAH), and epidural hematoma. This ordinal model is more discriminative and has been shown to have better predictive value for outcome when compared to the Marshall score; however, it is still not widely used in clinical practice.[31,32]

Neuroimaging has a key role in diagnosis of NW.[4] The progression or presence of new lesions on follow-up CT scan is an NW definition by itself.[4,9] Radiological worsening may anticipate or present simultaneously with clinical worsening.[4,9] As a general rule, a deterioration in CT scan even without changes in neurologic examination must be a warning signal for closer monitoring.

The criteria employed to define radiological NW (**Fig. 1**) are[4,9]

- New space-occupying lesion.
- Increase in volume of previous lesion.
- New onset or increase in volume of cerebral edema.
- Basal cisterns compressed or absent (new onset or worsening of previous one).
- Midline shift increase.

According to the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) Pilot study in mild TBI, subjects with early NW showed a higher lesional burden in initial CT scan.[33] The most common associated injuries were subdural hematoma (SDH), SAH, cerebral contusions, and IVH.[33] Early NW was also

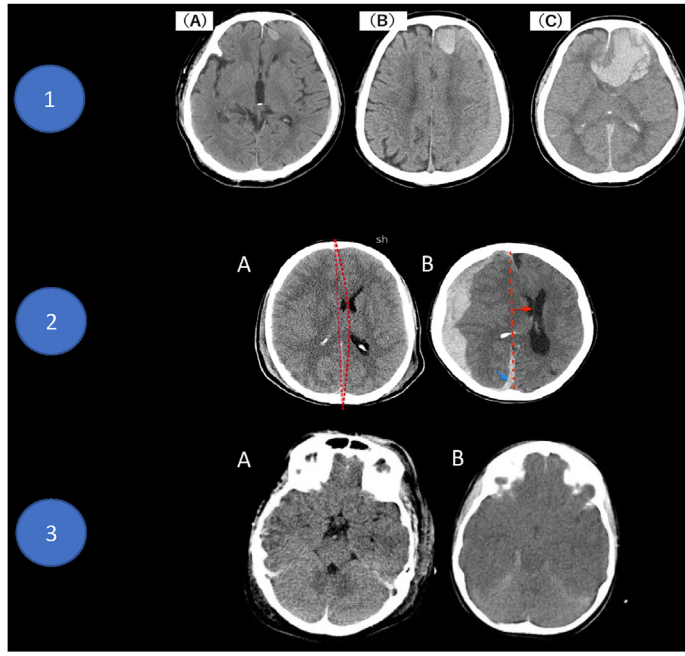

Fig. 1. Radiological NW criteria. (1) Cerebral Contusion. Progression of primary injury. (A) Admission; (B) 5 hours, and (C) 24 hours after admission. (2) Midline shift increase. (A) 4 hours after trauma, (B) 12 hours after trauma after clinical deterioration (decrease 2 points in motor GCS). (3) Basal Cisterns obliteration. (A) 1 hour after TBI and (B) 14 hours after admission.

associated with signs of high intracranial pressure (ICP) such as midline shift (50%), cisternal compression (56%), and cerebral edema (69%).[33]

Neuroworsening Detected by Cerebral Monitoring

The pathophysiology of MoTBI does not differ in any way than in severe TBI.[3] After the trauma and according to its kinetics, a series of lesions that constitute the "primary injury" develop macroscopically and microscopically.[2,3,25,26]

Simultaneously and consecutively, a series of intracranial phenomena and cascades (inflammation, coagulation, endocrine, and metabolic) are triggered and, depending on the type, magnitude, and severity of the initial damage, will contribute to the development of different forms of secondary injury, among which intracranial hypertension, cerebral tissue hypoxia, metabolic crises, and cerebral energy dysfunction are the most common and dangerous.[2,3,25,26]

Over the last years, the development of new monitoring techniques (invasive and noninvasive) have allowed, through the information obtained, the integration and deep analysis in real time of pathophysiological changes occurring in the injured brain.[1,25,26,34,35]

A recent systematic review and metanalysis of patients with MoTBI showed that invasive ICP monitoring was used in 18.3% (95% confidence interval [CI]: 8.1%–36.1%) of cases, and intracranial hypertension was documented in 44% (95% CI: 33.8%–54.7%) of monitored patients.[36] ICP monitoring was performed in 32.2% of patients with a GCS of 10 or less versus 15.2% of patients with GCS greater than

10 ($P = .59$).[36] However, the studies included in the systematic review were highly heterogeneous and the risk of bias was high. No variables associated with use of ICP monitoring or detection of intracranial hypertension were found.[36] At present, there are no studies regarding the use of invasive cerebral oxygenation monitoring in patients with MoTBI.

Noninvasive neuromonitoring are promising tools that can help in the categorization and follow-up of patients with MoTBI and can potentially add important information to prevent and diagnose NW. Several techniques are available and others are in development. Measurements of the optic nerve sheath diameter (ONSD) using ultrasound correlate with an increased ICP, particularly when using a threshold of ONSD greater than 6 mm.[37]

Recently, a technique based on the detection of microexpansions of the cranial vault was shown to be able to reliably display the morphology of the ICP wave; the relationship between the P1 and P2 components and the time for the peak of the wave had good correlation with invasive ICP values.[38,39] Although it is a developing technique, growing evidence is promising.[38,39] Because this modality is exquisitely sensitive to motion, it is only reliable in sedated (and ideally paralyzed) patients.

Bouzat and colleagues[40] studied the role of transcranial Doppler (TCD) in the prediction of NW and outcome of mild and MoTBI. Normal TCD was considered when values of pulsatility index were less than 1.25 and diastolic blood flow velocity was higher than 25 cm/s in both middle cerebral arteries.[40] In this study, 6% of 356 patients developed NW,[40] and TCD had 80% sensitivity (95% CI: 56%–94%) and 79% specificity (95% CI: 74%–83%) to predict NW.[40]

The American Nurse Association recently published a prospective observational study in patients with TBI evaluating the correlation between NW (defined as deterioration of 2 or more points in total sum of GCS) and Neurologic Pupil index (NPi) measured by quantitative pupillometry in the first 24 hours after admission.[41] There was a significant association between NPi less than 3 and NW ($P < .0001$).[41] The sensitivity of the NPi to detect NW was 51.4% and the specificity was 91.7%.[41]

In summary, in individuals monitored either invasively or noninvasively, alterations in neuromonitoring parameters may denote a deterioration in the clinical condition, which should trigger the necessary measures to detect and correct the possible cause(s) that originate it. The Latin American consensus of MoTBI suggests the following criteria of NW in the variables obtained from monitoring[4]:

- Pulsatility index in TCD greater than 1.4
- ONSD greater than 5 mm
- Pupillometry (NPI <3)
- Change ICP waveform (P2 > o = P1) invasive or noninvasive
- ICP greater than 22 mm Hg
- $PbtO_2$ less than 20 mm Hg
- $SjVO_2$ less than 50%
- Noninvasive cerebral oxygenation near infrared spectroscopy (NIRS) < than 50%
- Epileptic discharges in electroencephalogram monitoring

Integrative Definition of Neuroworsening

Integrating the above criteria, the Latin American consensus proposes the following definition[4]:

In MoTBI, NW is defined as "*the deterioration in 1 or more of the following* baseline characteristics: clinical, imaging, or neuromonitoring status (invasive or noninvasive), sufficient to require medical or surgical therapy."

CAUSES AND TIMING OF NEUROWORSENING AFTER MODERATE TRAUMATIC BRAIN INJURY

NW can appear at any time during the evolution of the TBI. The literature describes 2 main periods for deterioration, "early or late," depending on whether it occurs before or after 72 hours after injury.[9,11,17]

In general, the causes of NW follow specific pathophysiological changes. Basically, we can identify 3 principal events.

a. *Progression of the primary injury* (SDH, extradural hemorrhage [EDH], and contusions). In 1975, a group of individuals (most of them with epidural hematomas) was described under the acronym "talk and died," characterized by initially presenting a score in the verbal component of the GCS of 3 or more points, but who subsequently deteriorated and died, generally due to potentially reversible causes.[42] Most of these patients belonged to the "moderate" group.[43–48] Increase in size of cerebral contusions is an important risk factor for NW within the first 1 to 2 days after trauma.[49]
b. *Secondary insults*, which may originate following intracranial complications (intracranial hypertension, tissue hypoxia, cerebral edema, appearance of new lesions, seizures, sympathetic hyperactivity, vasospasm, spreading depression, and hydrocephalus) or extracranial causes (arterial hypotension, hypoxemia, hypercapnia, intrathoracic or intra-abdominal hypertension, hypoglycemia, hypocapnia, and hyperthermia).[9,11]
c. *Iatrogenic*, which include adverse effects from drugs (sedatives, analgesics, osmotherapy agents, and vasopressors), complications of mechanical ventilation (inadequate ventilation or high intrathoracic pressures and oxygen toxicity), and sepsis (vascular catheters, neuromonitoring devices, and pneumonia).[9]

Another way to categorize the causes of NW is according to their origin. Neurologic and nonneurological causes can be recognized. In MoTBI, neurologic causes are more frequent in the "early" period, mainly driven by the appearance of new intracranial lesions or to the progression of mass effect.[9,11–13]

HOW OFTEN DOES NEUROWORSENING OCCUR IN MODERATE TRAUMATIC BRAIN INJURY?

The prevalence of NW after MoTBI is far from negligible, estimated at 1 every 4 patients. Analyzed series have showed a prevalence that ranges between 12% and 49.6%, averaging 28%.[12,13,17–19,50,51]

RISK FACTORS FOR NEUROWORSENING IN MODERATE TRAUMATIC BRAIN INJURY

In MoTBI, the available literature is scarce and present multiple and varied methodological limitations. Chen and colleagues[18] in a Chinese retrospective series that included 479 patients with MoTBI studied different clinical, radiological, and laboratory parameters evaluated at hospital admission as potential predictors of NW. In the multivariate logistic regression analysis, the following factors were found to be associated with worse outcome[18]: presence of arterial hypertension; Marshall's CT scale types III and IV; SDH, frontal and temporal contusions, Injury Severity Score greater than 13, D-dimer level greater than 11.4 mg/L, GCS less than 10 points, and platelet count less than 152,000/mm^3.

Based on these findings, the aforementioned group created a prediction model, which is presented in a nomogram.[18] The prediction model was first internally

validated and showed that the C-statistic of the prediction model was 0.881 (95% CI: 0.849–0.909). External validation showed that the nomogram could predict NW with an area under the curve (AUC) of 0.827 (95% CI: 0.763–0.880).[18]

A Latin American series that included 232 individuals (Godoy DA, data not yet published, 2024) identified in the multivariate analysis the following risk factors associated with NW: GCS (odds ratio [OR]: 0.50; 95% CI: 0.28–0.96), Marshall CT score (OR: 2.34; 95% CI: 1.25–4.35), contusions (OR: 3.06; 95% CI: 1.53–20.07), temporal location of the contusion (OR: 3.61; 95% CI: 1.39–9.67), presence of multiple contusions (OR: 2.79; 95% CI: 1.33–5.82), and extracranial injuries (OR: 2.79; 95% CI: 1.33–5.82). With these parameters, the authors developed a score that showed 85% accuracy. However, this prediction model needs external validation.

Other NW risk factors described in literature include age greater than 65 years; heart rate, mean arterial pressure, and temperature variability (based on activation of sympathetic system); and infections and coagulopathy.[33,52]

Godoy and colleagues[10,53] proposed a simple and practical way to categorize risk groups in MoTBI, including GCS and Marshall CT scale into the so-called traffic light method. According to this method, when the score in the Marshall scale is III or IV and the GCS is below 11, the risk of NW increases ("red light") and the patient should undergo strict neuromonitoring in the intensive care unit (ICU).[10,53]

DO BIOMARKERS HAVE A ROLE IN NEUROWORSENING PREDICTION?

Biomarkers (BMs) are molecules that reflect important pathophysiological processes.[54–56] After TBI, proteomic BMs are secreted into the circulatory system.[57] BMs can be an auxiliary tool to categorize the severity and the risk of TBI progression.[54–56] BMs have demonstrated to have good ability to predict outcome[54–56] and can be useful as noninvasive neuromonitoring tools.[58] Many of these markers are specific to neuronal cells, and others to glia or axons, reflecting damage to different components of the brain parenchyma.[54–56] Some BMs reflect blood–brain barrier damage or inflammation.[54–56] S 100 beta protein, neuron-specific enolase, glial fibrillary acid protein (GFAP), and ubiquitin C-terminal hydrolase-L1 (UCH-L1) are the most commonly investigated BMs.[59,60] Recently, neurofilament light chain (NFL), an intermediate filament protein abundantly expressed in subcortical axons, has been studied as a prognostic biomarker in TBI.[61]

The initial levels and temporal profile of a panel of BMs can characterize the severity of brain damage.[60] In a CENTER-TBI study, Whitehouse and colleagues[62] showed that BM concentrations are associated with lesional burden: parenchymal injuries have higher concentrations than extraparenchymal injuries. UCH-L1 primarily increases in diffuse injury, while GFAP shows higher levels in focal mass lesions.[63] Interestingly, some BMs are elevated despite normal CT scan.[62] GFAP and UCH-L1 appear to be elevated in patients with MoTBI without CT scan findings but with evidence of injury on MRI.[64] These BMs might be elevated in occult neurologic injuries such as patients with persistent postconcussion syndrome and negative neuroimaging.[62] TAU and NFL are promising BMs to assess the severity of diffuse axonal injury.[62] Also, BMs of systemic metabolic stress are consistently associated with worse prognosis, compared to patients with normal metabolic profile.[65]

Yet, some important open questions remain to be elucidated before BM can be recommended for use in daily clinical practice, such as (1) is the optimal set of BM? (2) Is it necessary to measure BM in cerebrospinal fluid or is it sufficient measuring them in serum? (3) Which is the kinetics of BMs (production, elimination, and half-life); and

(4) which is the most appropriate timing for initial and following sampling of BMs.[1–3,8] Additionally, the accuracy of BMs for prediction of long-term outcomes and their association with the severity of the injury are only modest at present.[54,56,66]

Despite these uncertainties, BMs have a huge potential for recognizing the risk of NW at an early stage, and thus guide the use of neuromonitoring. We think that BM will be soon incorporated into the decision-making algorithm for patients with MoTBI.[66]

WHAT IS THE IMPACT OF NEUROWORSENING ON THE OUTCOME OF PATIENTS WITH TRAUMATIC BRAIN INJURY?

NW has a profound negative impact on patients' outcome and has been associated with greater mortality and high burden of moderate and severe neurologic disability after severe TBI.[11,12] The Selfotel and Tirilazad trials demonstrated that mortality and poor outcomes (evaluated as glasgow outcome score GOS] at 6 months) were clearly higher among patients who had NW ($P < .001$).[11,12] Compagnone and colleagues[17] also found higher risk of poor clinical outcomes in patients with NW (OR: 3.24; 95% CI: 1.65–6.39; $P = .0004$). Similar findings were noted in other cohorts, where NW was independently associated with death or severe disability.[50,67]

According to TRACK-TBI study, individuals with NW showed higher in-hospital mortality (37.5% vs 0.6%; $P < .001$) and unfavorable 3 and 6 month outcomes (58.3%/4.9%; 53.8%/6.2%; all $P < .001$)[33] compared to those who did not have NW.

HOW TO APPROACH PATIENTS WITH NEUROWORSENING?

NW is often a neurologic and neurosurgical emergency.[4,9] Therefore, clinicians have to pay close attention to diagnose NW early and treat its possible causes.[3,4,9,10]

The recent Latin-American MoTBI consensus suggests the institutional development of surveillance, detection, and early action protocols for NW.[4]

In many hospitals, patients with MoTBI are not routinely admitted to the ICU.[4] If the neurologic examination, initial CT scan and vital signs are normal, usually these patients are managed in the first hours (or even days) in the emergency department. However, during this window of time, the patient may deteriorate. Noninvasive neuromonitoring can be helpful to follow up this group of patients.[4]

The alarm level should never be lowered. Management hinges on serial clinical examination and achieving physiologic homeostasis, avoiding secondary insults of systemic origin.[4] It is important to ensure the ABCs of trauma, evaluating and taking the necessary measures to maintain adequate airway, ventilation, and systemic oxygenation,[3,4] to avoid arterial hypotension, hypoglycemia, and correct any abnormal physiologic parameters.[3,4,68]

In agitated patients who require sedation after adopting nonpharmacological measures, we recommend a "cooperative" regimen that avoids obscuring the clinical neurologic examination while maintaining cardiorespiratory stability.[69]

The optimal strategy for radiological monitoring is unclear.[4] Recent consensus suggests performing a follow-up scan at 6 to 8 hours if the patient is admitted within 6 hours of the trauma.[4] Subsequently, a new CT is recommended at 24 hours after admission if the patient does not develop NW.[4]

It is also crucial to appropriately triage patients who necessitate ICU admission because of high risk of NW. In this context, the traffic light method is an easy, simple, and practical tool to categorize the risk.[10] In general, patients with MoTBI with positive CT scan should be admitted to ICU[3,4,10,70] in order to receive a more intensive neuromonitoring assessment.[4]

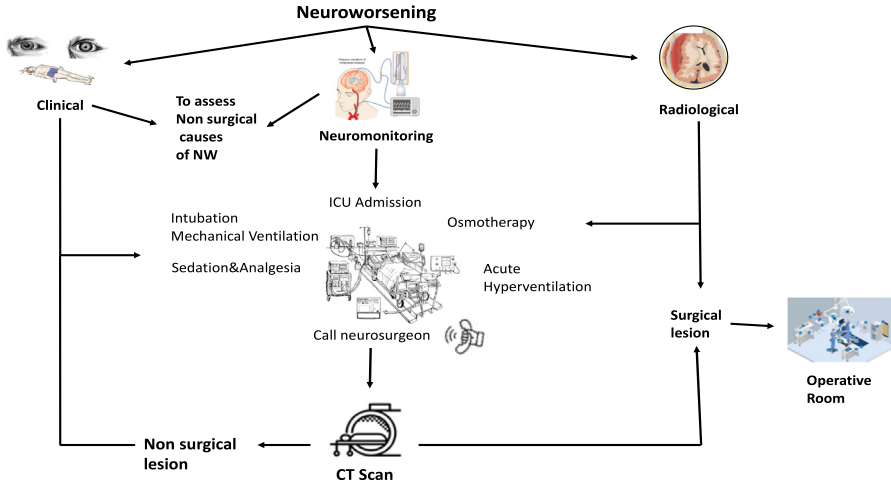

Fig. 2. NW approach. CT, computed tomography; ICU, intensive care unit; NW, neuroworsening.

The management of NW should be directed toward the determination of the cause, the treatment of intracranial hypertension, and neurosurgical intervention if needed based on imaging findings.[15,16] Intubation, mechanical ventilation, sedation and analgesia, osmotherapy, and hyperventilation should be considered in the acute phase.[16] If surgical lesion is excluded, invasive neuromonitoring may be useful[15,16] (**Fig. 2**).

SUMMARY

Patients with MoTBI are a high-risk group for the development of NW, and therefore, it is key to properly categorize them. Although a standardized and validated definition of NW is not available, NW can be defined in several ways (clinical, radiological, by invasive or noninvasive neuromonitoring) and generally denotes progression of the primary insult or occurrence of secondary intracranial or extracranial insults. It can occur at any time during the evolution of TBI. The most consistent risk factors are GCS and the type of injury detected on the CT scan. NW is not an uncommon complication of MoTBI, and its consequences are often devastating. Thus, it is imperative to develop surveillance, detection, and early management protocols to mitigate the effects of NW on the outcome of patients with TBI.

CLINICS CARE POINTS

- Patients with moderate Traumatic brain injury are at high risk of Neuroworsening.
- Literature is heterogeneous regarding the definition and the monitoring/treatment strategies of this population.
- Clinical examination and neuroimaging are fundamental to assess the risk of neuroworsening together with neuromonitoring and biomarkers.
- Research is warranted to provide evidence on the risk factors and predictors of Neuroworsening in moderate Traumetic brain injured patients.

DISCLOSURE

All authors declare that they have neither commercial nor financial conflicts of interest.

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Contemporary Management of Subdural Hematoma

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KEYWORDS

• Subdural hematoma • Medical management • Neurosurgery • Traumatic brain injury
• Guidelines • Middle meningeal artery embolization

KEY POINTS

- Acute and chronic subdural hematomas (cSDHs) represent distinct entities with different risk factors, etiologies, and treatment approaches.
- Both acute subdural hematoma (aSDH) and cSDH arise from trauma, but the mechanisms differ. While aSDH often results from tearing of bridging veins or injured cortical arteries, cSDH may evolve from minor trauma in the context of shearing of the dural border cell layer. Understanding the pathophysiologies that contribute to the formation and recurrence of hematomas provides insights into novel therapeutic paradigms.
- Surgical evacuation is the mainstay of treatment for aSDH, particularly in cases with significant clot thickness and/or midline shift. However, initial nonoperative management may be appropriate for selecting patients.
- The management of cSDH is evolving, with emerging evidence for some medical interventions such as statins and tranexamic acid. Middle meningeal artery embolization has revolutionized care for cSDH. Surgical drainage with the use of surgical adjuncts like drains and body temperature irrigation remain important considerations in patient management.

INTRODUCTION

Definition and Classification

A collection of blood in the space between the dura and arachnoid mater is called a subdural hematoma (SDH). SDH typically manifests as a crescent shape in noninvasive imaging modalities, traversing the adherent suture–dural junctions of the calvarium while being confined within the boundaries of the falx cerebri and the tentorium cerebelli (**Fig. 1**). SDH can manifest as either acute (aSDH) or chronic (cSDH), each representing distinct entities on a disease spectrum with varying risk factors, etiologies, and treatment paradigms.

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Neurol Clin 43 (2025) 65–78
https://doi.org/10.1016/j.ncl.2024.07.003 **neurologic.theclinics.com**
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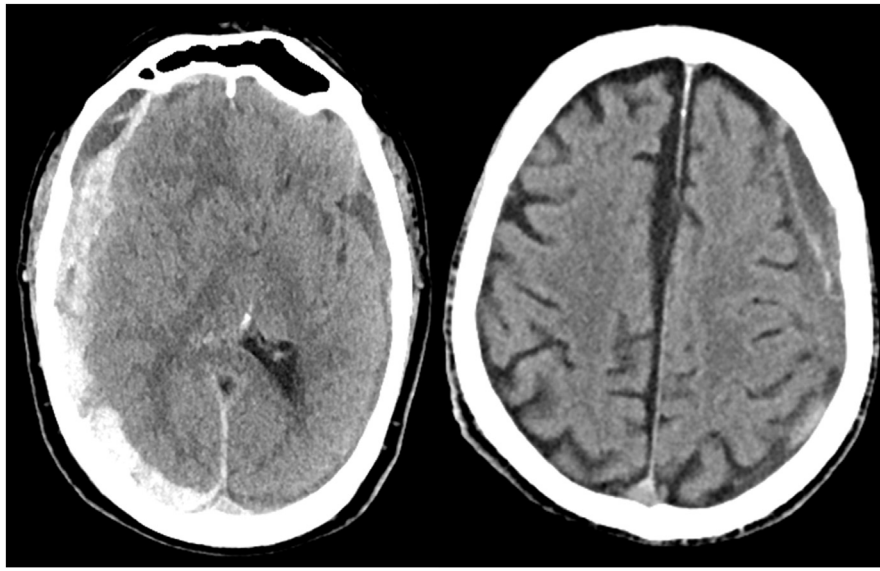

Fig. 1. *Left*: Right-sided subdural hematoma in an anticoagulated patient with mixed fluid density indicating acute and hyperacute blood products. *Right*: Chronic-appearing, isodense, left-sided subdural hematoma with a prominent hyperdense membrane coursing through the lesion.

Epidemiology

aSDH occurs in up to one-third of severe traumatic brain injury cases[1] whereas the incidence of cSDH has been reported to be between 1.7 and 79.4 per 100,000 persons per year.[2–4] The incidence of cSDH appears to be increasing over time, perhaps due to the more widespread use of noninvasive neuroimaging modalities, and is directly related to the rates of traumatic brain injury as well as increasing age.[5] Risk factors for aSDH include high-energy trauma, male gender, and age less than 50 years whereas risk factors for cSDH include advanced age (>60 years),[5] cerebral atrophy,[6] and blood thinning agents.[7]

Pathophysiology

Acute subdural hematoma. The most common etiology of aSDH is trauma, and the extent of superimposed traumatic brain injury contributes significantly to the clinical presentation and prognosis of the patient. The classic model for aSDH formation is tearing of bridging veins that are traversing the cortical surface into the dural sinuses. However, a significant number of aSDH are due to injured cortical arteries that bleed into the subdural space.[8] Given the considerably higher arterial pressure relative to intracranial pressure (ICP), it becomes readily apparent how a ruptured cortical artery could swiftly accumulate blood within the subdural space. Less obvious is how a torn vein, with its considerably lower cerebral venous pressure, could accumulate a substantial aSDH before being tamponaded by the clot itself and the resultant rising ICP.[9] It has been proposed that bridging veins are susceptible to shearing within the dural border cell layer of the dura mater.[10] This shearing leads to an unraveling of the delicate dural border cell layer. Paradoxically, the rising ICP would correspondingly elevate intracranial venous pressure,[11–13] thus enlarging the hematoma.[9] Therefore, despite the differences in venous and arterial pressure, aSDH from either a bleeding cortical artery or bridging vein may have a similar result.

Chronic subdural hematoma. In general, cSDH is the result of trauma. While some cases of cSDH evolve from liquefaction of a known aSDH, in many cases of newly diagnosed cSDH, the preceding trauma is often so minor that patients may not recall an inciting event. Because cSDH is exponentially more prevalent in patients with advanced age, a possible link between age and cSDH is via cerebral atrophy, which may result in tension on the bridging veins, making them more susceptible to injury from relatively minor trauma.

The subdural space is bounded by dural border cells which, when sheared from even minor trauma, leak blood into the subdural space due to their thin bridging/traversing veins.[10,14,15] This expands the potential space and results in release of cytokines from the dural border cells, attracting fibroblasts, which form thick outer and thin inner membranes of the hematoma cavity. Due to a reactive inflammatory cascade and release of angiogenic factors, the outer membrane forms abundant, fragile blood vessels with highly permeable capillaries, leaking blood into the subdural space.[16] Blood in the subdural space clots and then eventually undergoes fibrinolysis,[17,18] which stimulates a local inflammatory response,[19–23] and results in recurrent hemorrhage into the subdural space from the leaky capillaries of the outer membrane.[24,25]

In a patient who presents with nontraumatic, bilateral subdural fluid collections that are chronic-appearing or of mixed density, evaluation for an occult cerebrospinal fluid leak may be necessary if the patient endorses typical symptoms, such as a clear postural (orthostatic) headache.

MANAGEMENT

Acute Subdural Hematoma

According to guidelines published from a panel of neurosurgical experts,[26] surgical evacuation is indicated for

1. Patients with an acute subdural hematoma with clot thickness greater than 10 mm or with midline shift greater than 5 mm on computed tomography regardless of the patient's Glasgow Coma Scale (GCS) score.
2. Patients with a GCS score less than 9 with an aSDH less than 10 mm thick and midline shift less than 5 mm if the GCS score decreases by 2 or more points between the time of injury and hospital admission and/or if the patient presents with asymmetric or fixed/dilated pupils and/or if the ICP exceeds 20 mm Hg.

When surgery is indicated for aSDH, it should occur without delay.

Not all cases of aSDH require emergent neurosurgical intervention, however. In a real world analysis of 869 patients presenting with aSDH, 74.3% were initially managed nonoperatively with only 6.5% of those patients requiring delayed surgery.[27] Patients appropriate for initial nonoperative management tended to have small (maximal thickness <10 mm) SDH, were asymptomatic, or were very elderly with minimal symptoms. Thicker SDH, greater midline shift, convexity location, history of alcohol abuse, and history of falls were associated with need for delayed surgery.

aSDH patients selected for nonoperative management are generally admitted to the intensive care unit for close neurologic observation.[27] ICP monitoring is indicated for those patients whose GCS score is 8 or less who have an abnormal scan (including an aSDH that does not meet strict operative criteria).[26] Prophylactic anti-epileptic therapy is indicated for a 7 day duration for patients with aSDH[28,29] using either levetiracetam or fosphenytoin.[30] In patients who are immobile, prophylaxis for venous thromboembolism can be initiated with either low-molecular-weight heparin or unfractionated heparin 24 hours after stable head computed tomography.[31,32]

For patients with aSDH in whom emergent surgery is warranted, surgery may proceed with either a standard reverse question mark, retroauricular, or T-shaped Kempe incision based on surgeon's preference, history of prior scalp incisions, and need for future extracranial-to-intracranial bypass surgery.[33,34] Because aSDH often coincides with sequalae of severe traumatic brain injury, including parenchymal injury and diffuse cerebral edema, it is essential to plan for a large, unilateral frontotemporoparietal bone flap in accordance with the Brain Trauma Foundation TBI Guidelines.[35] When brain swelling after hematoma evacuation prevents safe replacement of the bone flap, a craniectomy is performed, necessitating cranioplasty for skull reconstruction weeks to months after the initial surgery. Because decompressive hemicraniectomy has been shown to reduce mortality in cases of refractory posttraumatic intracranial hypertension,[36] there has been some controversy[37] as to whether a craniectomy should be pre-emptively performed when evacuating aSDH in anticipation of delayed cerebral edema and elevated intracranial hypertension given the risks associated with cranioplasty.[38] In a recent multicenter, randomized, controlled trial comparing outcomes of craniotomy versus craniectomy in adult patients with traumatic aSDH,[39] the investigators found no difference in disability or quality of life outcomes between the groups but there was a higher rate of additional surgery (namely craniectomies) within 2 weeks of the initial surgery in the craniotomy group as compared to the craniectomy group (14.6% vs 6.9%), and a 3 fold increase in wound complications in the craniectomy group as compared to the craniotomy group (12.2% vs 3.9%).

Postoperatively, anti-seizure prophylaxis is generally continued for a total of 7 days. That said, seizures or epileptiform changes on electroencephalogram are observed during the acute postoperative period in approximately 25% of patients[40] and, in such cases, antiepileptic management is typically escalated and continued for a minimum of 3 months. Initiation of venous thromboembolism (VTE) prophylaxis is more precarious as compared to patients with aSDH managed nonoperatively. A large retrospective cohort study investigated the timing of VTE prophylaxis in adult patients after urgent neurosurgical intervention for TBI in relation to thromboembolic and intracranial complications.[41] Early initiation (during the first 3 postoperative days) of VTE prophylaxis was associated with reduced risk of thromboembolism but also increased risk of additional neurosurgical intervention, highlighting the delicate balance between intracranial bleeding and peripheral clotting in these delicate patients.

Chronic Subdural Hematoma

Management of patients with cSDH is much more nuanced due to the fact that many patients are elderly with multiple comorbidities, are often asymptomatic or minimally symptomatic, and because of additional interventions available for cSDH, particularly middle meningeal artery embolization (MMAe), which has revolutionized care for patients with cSDH. As cSDH is thought to derive from fragile, inflamed vascularized neomembranes supplied by the MMA,[42,43] non-operative interventions have been employed to target the inflammatory or angiogenic etiologies of cSDH.

Medical treatment of chronic subdural hematoma

The 3 most extensively studied medical interventions for cSDH are corticosteroids, atorvastatin, and tranexamic acid (TXA).[44] Steroids are thought to inhibit the formation of neomembranes and neovessels and systematic reviews suggested that steroids may prevent the need for surgical intervention and reduce the risk of recurrence after cSDH drainage.[45,46] In 2020, a multicenter, randomized trial aimed to determine the effects of dexamethasone treatment on outcomes in patients with symptomatic cSDH.[47] Of the 748 patients enrolled, 94.2% underwent surgical evacuation of the

hematoma. Fewer patients in the group treated with steroids reported a favorable outcome (modified rankin scale [mRS] 0–3) as compared to the control group (83.9% vs 90.3%); however, the incidence of repeat surgery for hematoma recurrence was much lower in the dexamethasone group as compared to the placebo group (1.7% vs 7.1%). The incidence of serious adverse events was greater in the dexamethasone group as compared to the placebo group (16.0% vs 6.4%). An additional multicenter, randomized trial was published in 2023 that sought to determine whether dexamethasone as a stand-alone therapy had the same potential to achieve favorable outcomes as surgical evacuation in patients with symptomatic cSDH.[48] This trial was stopped early because of safety and outcome concerns in those patients treated with steroids. Specifically, the odds ratio for an mRS 0 to 3 at 3 months with steroids versus surgery was 0.55 (95% confidence interval, 0.34–0.90), complications occurred in nearly twice as many steroid-treated patients (59% vs 32%), and the need for additional surgery was 9 times greater in the steroid group (55% vs 6%). Thus, steroids are not recommended for use in cSDH.

Statins, whose canonical function is to reduce low-density lipoprotein cholesterol in patients with hyperlipidemia, are also thought to inhibit inflammation and immature angiogenesis in the neomembranes of cSDH.[49] The results of a multicenter, randomized, phase II clinical trial investigating the safety and efficacy of 20 mg atorvastatin daily for 8 weeks versus placebo in cSDH treated nonoperatively were reported in 2018.[50] Patients in the atorvastatin group saw greater reduction in hematoma volume, had significantly improved neurologic function, and underwent less surgery for enlarging hematoma and/or deteriorating neurologic condition, together suggesting a possible role for atorvastatin in the nonsurgical treatment of patients with cSDH. The phase III trial is currently underway (NCT03956368).

TXA inhibits fibrinolysis by blocking the lysine receptor on plasminogen and plasmin. There have been reports of TXA being safe and effective for the treatment of cSDH both as stand-alone therapy[51] and in combination with surgery.[52] As to the latter point, an observational study with propensity score matching of patients undergoing surgery for cSDH showed that the reoperation rate was markedly lower in patients treated with TXA (1.9% vs 6.1%) with no difference in adverse events. There is one active and one pending clinical trial investigating the role of TXA in cSDH hematoma: the TXA to prevent operation in chronic subdural hematoma (TORCH) trial[53] (NCT03582293) and the use of TXA in the treatment of symptomatic subdural hematoma (TRACE) trial (NCT05713630).

Middle meningeal artery embolization

Few interventions have revolutionized the management of any medical ailment the way that MMAe has impacted care of patients with cSDH.[54] While MMAe has gained widespread traction over the past 5 years, the first reported case of MMAe was performed in Japan in 2000.[55] The zeitgeist at the turn of the century was that cSDH originated from venous bleeding. Therefore, the rationale to embolize an artery—particularly the MMA, which is implicated in epidural rather than subdural hematomas—in the treatment of cSDH was, by all accounts, illogical. Yet the pioneers of MMAe were able to avoid being trapped by dogma and create a paradigm shift by combining 3 key observations. First, diffuse dilation of the ipsilateral MMA with scattered abnormal vascular networks was seen in patients with cSDH who underwent catheter angiography.[56] Second, cSDH accumulates contrast material administered systemically, suggesting a connection between the systemic vasculature and the hematoma.[55] Third, MMAe was an established procedure for preoperative embolization of meningiomas and, thus, interventionalists were familiar with the approach and safety had already been established.

The first large case series of MMAe for cSDH was published in 2017, comparing 72 prospectively enrolled patients with cSDH who underwent MMAe either as stand-alone therapy or in conjunction with surgery against a historical control group of 469 patients who were either managed with close observation or surgery.[57] The authors reported spontaneous resolution of all asymptomatic patients who underwent stand-alone MMAe and a marked reduction in need for rescue surgery in patients receiving MMAe as compared to the historical control cohort (1.4% vs 18.8%). Since then, there has been an explosion of articles published about MMAe for cSDH.[54,58] A recent systematic review and meta-analysis analyzed outcomes in cSDH patients treated with MMAe to those without.[59] The authors identified 9 observational studies including 1523 patients of which 337 received MMAe. They reported a significant reduction with MMAe versus conventional management in terms of treatment failure (5.6% vs 22.2%) and need for surgical rescue (4.1% vs 16.1%), higher chance of complete hematoma resolution with MMAe versus conventional management (61.9% vs 26.4%), and no difference in complication rates, hospital length of stay, functional outcomes, or mortality. The results of 3 major trials (EMBOLISE, MAGIC-MT, and STEM) were recently presented at a major international meeting.[60] Based on the data presented, these studies are the first Level 1A evidence to show that MMAe, whether used alone or as a surgical adjuvant, prevents cSDH recurrence or progression and significantly reduce the need for repeat cSDH drainage and should therefore be routinely used in the care of patients with cSDH.

There has been growing interest recently as to the safety, feasibility, and efficacy of MMAe across multiple classes of embolic materials including liquids, particles, coils, and combinations thereof.[61] Polyvinyl alcohol (PVA) particles, flow-directed materials that result in mechanical obstruction of the artery, have been the most common embolic agent used in studies investigating MMAe for treating cSDH.[62] PVA particles have a few distinct advantages. First, as they are flow-directed, the microcatheter can sit in the proximal MMA or just distal to the foramen spinosum where the outer diameter of the microcatheter is less than the inner diameter of the artery to facilitate distal flow of the particles. Second, PVA particles are small enough to travel into the distal MMA branches yet large enough to avoid entering the dangerous extracranial–intracranial (EC-IC) anastomoses of the MMA,[63] namely collateralization with the internal carotid artery through its cavernous branch, ophthalmic anastomosis via the lacrimal artery, and facial arcade by way of the petrosal branch. Third, procedural pain is generally minimal with particle embolization of the MMA and can be performed in most patients without general anesthesia. However, PVA particles tend to aggregate proximal to the intended target, which can result in distal recanalization through neoangiogenesis and they are radiolucent and cannot be directly visualized. These particles may also reflux since the microcatheter is not wedged into the distal MMA.

Liquid embolic agents (Onyx, N-butyl-2cyanoacrylate/TruFill, Squid, PHIL), on the other hand, address many of the disadvantages of particles. Liquid agents tend to penetrate much deeper into the vessel than particles, they result in a more durable embolization, and they are opacified, allowing the operator to see exactly where the embolisate is at all times. However, liquid agents can be pushed through angiographically invisible EC-IC anastomoses, and can lead to stroke, blindness, and/or permanent facial nerve paralysis if the microcatheter is not wedged beyond these tiny collaterals. Furthermore, many of the liquid agents require vehicle delivery in dimethyl sulfoxide, which can be painful for patients, necessitating either general anesthesia or conscious sedation. An active area of interest and investigation is comparing the safety and efficacy of particle versus liquid agent embolization for patients with cSDH, although preliminary analysis seem to indicate that both agents are safe and effective with nearly identical outcomes.[64–68]

Surgery

Traditionally, surgery for cSDH has included twist drill craniotomy, burr hole craniostomy, or craniotomy/mini-craniotomy.[69] The goal of each procedure is the same—to evacuate the hematoma—but patient-specific, hematoma-specific, and/or surgeon-specific factors may influence the selection of one technique over the others. Twist drill craniostomy is a bedside procedure performed under local anesthetic often reserved for patients who are otherwise not appropriate for general anesthesia and for patients with highly liquefied cSDH without many intervening membranes. Burr hole craniostomy is the most frequently used and most studied surgical intervention for patients with cSDH.[69] Usually 2 large (>2.5 cm) burr holes[70] are drilled over the cerebral convexity followed by a cruciate durotomy to access the subdural space. Copious irrigation is then used to clear the subdural space of hemorrhagic debris. Finally, a conventional craniotomy or mini craniotomy may seldom be needed for subdurals with extensive membranes or for mixed hematomas with a significant acute component. Although most neurosurgeons use the 2 burr hole craniostomy technique, multiple systematic reviews and meta-analyses have failed to consistently demonstrate clear superiority of any one technique[69,71,72] and, therefore, treatment can be tailored to the individual patient and clinical scenario.

There are 2 surgical adjuncts that have been shown to significantly reduce hematoma recurrence after cSDH surgery: drains and body temperature irrigation. In 2009, a randomized controlled trial of adult patients undergoing burr hole drainage of cSDH demonstrated clear superiority of subdural drain placement as compared to no drain.[73] The authors found that 9.3% of patients with a subdural drain had a recurrent hematoma requiring redrainage versus 24.0% of patients without a drain. Additionally, patients who had a subdural drain placed had a significant reduction in mortality at 6 months postoperatively (8.6% vs 18.1%). Because placement of a subdural drain may be impossible in cases of rapid brain re-expansion or predispose to complications, namely injury to the brain parenchyma, various groups have investigated the utility of alternatively placed drains in the subgaleal/subperiosteal space[74,75] and have found subdural and subgaleal/subperiosteal drains to be interchangeable[76] in terms of reducing hematoma reaccumulation and mortality. A recent multicenter, randomized trial investigating the relationship between subdural drainage time and 3 month SDH recurrence found a 27% recurrence rate with 6 hours of postoperative drainage as compared to 20% with 12 hours and 10% with 24 hours, thus establishing 24 hours as the optimal postoperative drainage time following cSDH evacuation.[77] Warm, body-temperature irrigation fluid in the evacuation of cSDH has also been shown to significantly reduce hematoma recurrence.[78] In a 2023 multicenter randomized clinical trial of adult patients who underwent cSDH evacuation, patients in the body temperature irrigation fluid group had a significant reduction in recurrent hematoma requiring reoperation as compared to those with room temperature irrigation (6% vs 14%). These studies strongly suggest that in patients undergoing cSDH surgery, leaving a drain postoperatively (either a subdural drain or a subgaleal/subperiosteal drain) and body temperature irrigation intraoperatively should be standard of care.

Decision-making in chronic subdural hematoma

Unlike aSDH, there are no expert guidelines for the management of cSDH but some helpful contemporary decision algorithms for cSDH management have been proposed.[79] Prior to the widespread use of MMAe, most cSDHs were considered for surgery if the hematoma thickness exceeded 1 cm and/or midline shift exceeded 5 mm regardless of patient presentation. In the era of MMAe, however, there is a stronger focus on symptoms to decide whether surgery is needed. MMAe has shown to be

very safe and effective and can serve as the primary treatment of patients with asymptomatic or mildly symptomatic cSDH who can be monitored closely outside the hospital. Indeed, most cSDHs at our institution get MMAe unless the cSDH is found incidentally, the patient is completely asymptomatic, and the cSDH is small without any local mass effect. For patients who are symptomatic from their cSDH and/or have a cSDH that results in at least 5 mm of midline shift and/or if there is cortical flattening due to the size and mass effect of the cSDH, surgical evacuation is appropriate. In these cases, surgery should be performed with body temperature irrigation fluid, a subdural or subgaleal/subperiosteal drain should be placed, and, at centers with appropriate capabilities, adjuvant MMAe should be performed.

SUMMARY

aSDH and cSDH represent distinct entities on a disease spectrum with different epidemiologic patterns, risk factors, and treatment approaches. For aSDH, timely surgical intervention remains crucial, guided by established criteria such as clot thickness, midline shift, and neurologic status. However, nonoperative management may be an option for selecting patients, highlighting the importance of close monitoring and individualized decision-making. In contrast, the management of cSDH requires a more nuanced approach, considering the evolving therapeutic options. While surgical evacuation remains a cornerstone, recent advancements such as MMAe have transformed treatment paradigms, offering a less invasive yet highly effective alternative or adjunct to surgery. Additionally, medical interventions, namely statins and TXA may have a role in the future management of cSDH patients pending the results of ongoing clinical trials.

CLINICS CARE POINTS

- Management of acute subdural hematoma requires emergent evaluation by a neurosurgeon.
- Chronic SDH management has evolved over time, with middle meningeal artery embolization being more commonly used in these patients.
- Ultimate management for subdural hematoma requires review by a neurosurgon to determine if operative or non-operative management is appropriate.

DISCLOSURE

The authors have no granting organizations or grant numbers, contract numbers, or other sources of financial or material support to disclose. Declaration of AI and AI-assisted technologies in the writing process: During the preparation of this work, the authors used ChatGPT in order to assist in writing the abbreviations, abstract, key points, and summary sections of the article and to improve the clarity of a few selected sentences throughout the article to improve clarity and readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Brain Injury after Cardiac Arrest: Refining Prognosis

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KEYWORDS

• Coma • Cardiopulmonary resuscitation • Neurologic examination • Biomarkers • EEG • Neuroimaging

KEY POINTS

- Consolidation of several key clinical findings assessed over time is the preferred approach in prognostication.
- Bilateral absence of cortical (N20) responses is a strong indicator of poor prognosis but uncommon. The technique requires expertise and measures to reduce erroneous results.
- MRI may provide definitive findings of severe brain injury in some instances.
- Serum neuron-specific enolase and serum neurofilament light chain have some value but are not determinative.
- Antiseizure medications for epileptiform discharges or burst suppression may change EEG patterns but do not change outcome.
- Induced hypothermia does not improve outcome after CPR for a shockable rhythm. Fever control is common practice.

Neurologists consulting in intensive care units (ICUs) quickly discover that the prognostication of comatose patients after cardiopulmonary resuscitation (CPR) is one of the most frequently requested services. Annually, over 100,000 patients in the United States arrive in ICUs with anoxic–ischemic brain injury after CPR.[1] If performed by a trained bystander, CPR can restore circulation, but even with a timely hospital transfer, the odds of full recovery are slim. Survival rates at hospital discharge after out-of-hospital arrest remain 3% in Asia, 7% in North America, 8% in Europe, and 10% in Australia; overall, these represent frustratingly low rates.[2] If the chest compressions are not fast enough (120 bpm) and deep enough, the effort may be inadequate. Naturally, the outcome of cardiac arrest also is much worse with no one immediately available to start chest compression before the emergency medical technician arrives. Early chest compressions and the use of automated external defibrillators correlate with increased survival. However, most patients in cardiac arrest have no shockable rhythms (22% in a large Danish Series),[3] and the chance of a favorable neurologic

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Neurol Clin 43 (2025) 79–90
https://doi.org/10.1016/j.ncl.2024.07.004 **neurologic.theclinics.com**
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outcome falls off to less than 50% if delay to defibrillation lasts longer than 5 minutes and 20% or less over 10 minutes.[4] Shockable rhythms are more common in patients with underlying cardiovascular disease but over time evolve into nonshockable asystole. Moreover, in-hospital cardiac arrest is more commonly due to a nonshockable rhythm and often results from pulmonary disease.[5]

After circulation has been restored and the patient has survived several hours, a clinical picture of postcardiac resuscitation syndrome may emerge. Patients may have major (possibly reversible) myocardial dysfunction, a systemic ischemic-reperfusion syndrome, intravascular volume depletion, and acute coronary syndrome requiring emergent reperfusion therapy. Hemodynamics are often labile after cardiac arrest due to massive catecholamine release and myocardial stunning, and intravenous vasopressors and inotropes are necessary. Severe cases of persistent shock or hypoxia may warrant more invasive treatments such as intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO). Acute kidney injury and shocked liver can appear or develop over the following days,[6] causing the patient to become critically ill and comatose from the ensuing metabolic derangements. Then the neurologist is summoned to predict the clinical course.

It is a challenging question, but we and our colleagues must try to answer it. However, it is a struggle for many of us. Can we say that a cluster of certain clinical findings promises "reasonable" accuracy? In simple terms, cardiac arrest means no effective contraction of the heart muscle and no blood flow to the brain, which lead to sudden loss of consciousness. Halted blood flow injures the brain by depriving the brain's neurons of oxygen needed to function. Prolonged halted blood flow worsens the outcome. Brain injury occurs rapidly, and anoxia lasting 2 to 4 minutes activates biochemical mechanisms that cause irreversible neuronal damage. Selective neuronal vulnerability to this type of injury affects areas in the hippocampus, the CA-1 sector, the thalami, the neocortex, and the cerebellar Purkinje cells. Necrosis of the cortex is pathologically known as laminar necrosis. The presence of receptors for excitatory neurotransmitters or the high metabolic demands of these neurons may account for the vulnerability of these areas. Halted blood flow to the brain is the most severe diffuse brain injury and often the most devastating. Predictably, therapeutic interventions to protect the brain have been mostly futile.

The practice of prognostication has evolved over the years, but neurologists rely on basic principles of prognostication in comatose patients after CPR. They are (1) exclusion of confounders such as prior use of sedatives or neuromuscular blocking agents, severe hypothermia, and presence of organ failure (including shock); (2) identification of key poor prognostic signs such as myoclonus status, persistently absent pupil or corneal reflexes, sustained upward gaze, a motor response not better than extensor responses, or identification of possible loss of all brain function (brain death); (3) interpretation of abnormal laboratory tests such as absent cortical evoked potentials on somatosensory evoked potential (SSEP) studies and a rise in serum biomarkers such as neuron-specific enolase (NSE) and neurofilament light (NfL) chain; (4) understanding electroencephalography and assessment of seizures (or mimickers); and (5) detailed reading of neuroimaging. When asked to discuss the findings with family members, we must acknowledge uncertainty when pertinent but also authority when the chances of any acceptable outcome are indisputably slim. By necessity, the consulting neurologist is often the sole orchestrator of these conversations, which require skill and experience. We recognize the difficulty of this task when these 2 attributes are absent. But knowing all the odds, what can we truly contribute? In this article, I critically review prognostication, bring into focus its "refinement" over the decades, and provide a template for clinicians who must judge the functioning of patients

who awaken. We, neurologists, approach these patients with trepidation because we seldom know enough about the circumstances, the hospital course, and prior, sometimes critically essential details. Algorithms are inherently artificial, lack the necessary precision and performance, and never account for confounders and present or intercurrent medical illness. The key to good judgment is the evaluation of all the information; even then, we may need to observe the patient over a considerable number of days.

EARLIER STUDIES ON PROGNOSTICATION

For many years, we based outcome predictions on a prospective study of the neurologic examination and, more importantly, improvement in the first week.[7] Levy and colleagues[8] proposed distinctions that shifted the conversation. Patients without corneal reflexes, pupillary responses to light, or motor responses to pain after day 3 would not recover, whereas two-thirds of patients with spontaneous verbalization, orienting eye movements, eye opening to voice, or obeying limb commands regained independence within 1 year. Suddenly, 3 days seemed enough to ascertain the patient's chance to improve. However, a later study found less certainty with this time interval and the predictive value of motor response while still supporting the strong correlation of pupillary, corneal, and oculocephalic reflexes with prognosis.[9] The American Academy of Neurology practice parameter identified poor prognostication criteria but only in a small group of patients and restricted its conclusions due to the lack of studies with a high level of evidence.[10] Indicators of poor outcome after CPR were absent pupillary light response or corneal reflexes, extensor or no motor response to pain after 3 days of observation, and myoclonus status. Prognosis could not be based on circumstances of CPR (cardiac rhythm) or elevated body temperature. Bilateral absent cortical responses on SSEP studies recorded 3 days after CPR predicted poor outcome. Burst suppression or generalized epileptiform discharges on electroencephalogram (EEG) also predicted poor outcomes, but the literature did not provide sufficient prognostic accuracy. Serum NSE greater than 33 μg/L predicted a poor outcome. These guidelines were based on patients not treated with targeted temperature management (TTM) and were considered less valuable after the emergence of a general consensus that TTM changed outcome and, thus, prognostication. Moreover, listing the predictive value of separate prognostic factors was grossly misinterpreted as a justification of a unimodality approach, which was neither intended nor practiced.

Subsequent studies disputed the utility of TTM.[11] Many had already recognized that the early trials were insufficiently powered and had poorly defined or prescribed standardized care. Despite these flaws, TTM was seen for decades as a necessary approach to comatose patients after CPR, and the practice spawned a successful industry of cooling devices. Subanalysis of the TTM and TTM2 trials showed no benefit in patients with nonshockable rhythm. Hypothermia did not improve outcomes in trials of patients with in-hospital arrest. Moreover, the value of prolonged strict normothermia after out-of-hospital cardiac arrest was unproven.[12] Active, device-based fever prevention for 36 or 72 hours after cardiac arrest did not significantly change the percentages of patients dying or having severe disability or coma.[13] The hypothermia-treatment saga illustrates the overall concerns with critical care trials and how results were wrongly perceived as changing prognostication.[14] The rejection of hypothermia as an essential treatment changed the clinical approach to prognostication largely because extensive sedation and shivering treatments were discontinued. Interest in continuous EEG recordings (deficient data identified by the AAN 2006 guideline), serial

measurements of biomarkers, and more information on MRI opened the way to new guidelines and statements of scientific consensus.

RECENT REVIEWS AND ALGORITHMS

Prognostication on coma after CPR has been reviewed extensively in recent years, yielding a daunting number of review articles and opinion articles. Major changes have been a renewed interest in EEG patterns, new serum biomarkers, and larger series of patients with MR imaging. Little has changed in clinical assessment at presentation or assessment of different clinical trajectories. One of the first notable reviews was the 2014 European Resuscitation Council/European Society of Intensive Care Medicine Guideline,[15] which introduced several other factors indicative of a poor prognosis. These include early anoxic brain swelling visible on head computed tomography (CT), diffuse cortical restriction on diffusion-weighted imaging on MRI, absent cortical SSEPs, rising serum NSE, unreactive and burst-suppression EEG patterns or marked suppression to less than 20 μV,[16] and burst-suppression EEG time-locked with myoclonus status.[16–22]

While there are several recently published scientific statements and systematic reviews, no new definitive prognosticators have been identified over last 2 decades. The most recently published algorithm identifies the absence of motor responses or the presence of extensor responses to pain after excluding confounders as indicative of poor outcome,[17] discourages the use of a single value of NSE, and advises using multimodal prognostication. This scientific statement attempted further precision by introducing the terms "likely" or "very likely" poor outcome—determined by degree of false alarm or FPR—but key elements of prognostication have remained the same. A recent systematic review found higher likelihood of good neurologic outcomes for comatose survivors of cardiac arrest with the following: (1) an improving motor response to withdrawal to pain or localization to pain at 72 to 96 hours; (2) normal NSE blood values at 24 to 72 hours; (3) an SSEP N20 wave amplitude above 4 μV; and (4) continuous EEG background without discharges and absent diffusion restriction in the cortex or deep gray matter on MRI.[23] However, few patients meet all these criteria, and we have seen a number of patients still do poorly despite their presence, partly due to other medical complications. Neurologists recognize prediction is imperfect. Many reviews fail to advocate for neurologic expertise in prognostication and decision-making. Neurologic prognostication demands a detailed neurologic evaluation, and no laboratory test can or should replace it.

THE CLINICAL EVALUATION

Particular elements of the neurologic examination are vital when determining the severity of anoxic–ischemic injury. The standard clinical neurologic examination should include motor response to pain, with specific attention to myoclonus status, spontaneous or elicited eye-movement abnormalities, and brainstem reflexes. Brainstem reflex testing should include pupillary light reflex, corneal reflex, cough and gag reflexes, and assessing for spontaneous respirations. When evaluating the brainstem reflexes, we recognize that the brainstem is far more resilient to anoxic–ischemic injury than the cortex, and the pupil response to light is frequently within normal limits. Fixed and dilated pupils examined several hours postcardiac arrest are clinical indicators of a poor outcome, but they are rarely an isolated examination finding. They usually accompany additional signs of brainstem injury and occur in severe cases in which the patient requires prolonged or repeated resuscitation after initial resumption of circulation. Corneal reflexes may be absent (or minimally present) initially, often due

to prior anesthetic drugs but may return over time. They are notoriously difficult to judge in intensive care settings. Eye-movement abnormalities provide additional clinical information; for example, a persistent upward gaze indicates significant global bihemispheric injury, which may also involve the thalamus. Persistent upward gaze often indicates a poor outcome. When eliciting the vestibulo-ocular reflex or rapid head movement, the examiner may see a downward drift. Other eye abnormalities include the ping-pong gaze, lateral gaze deviations, or continuous blinking, which do not currently have recognized prognostic value.

An essential clinical indicator is myoclonus status, which is more clearly explained as continuous and forceful jerking movements involving facial muscles, limbs, and abdominal muscles.[24–26] These jerks can be provoked by touch, passive movement, or turning and may include the diaphragm, which affects the patient's ventilation. Myoclonus status signals a poor prognosis, and typically other clinical, electrophysiologic, and neuroimaging indicators of unfavorable prognosis are present. The presence of multisegmental myoclonus is always alarming. Myoclonus involves the face, limbs, and axial muscles in brief, spontaneous jerks. In the first hours after CPR, these jerks may be unrelenting and forceful. The patient may move in the bed—sometimes reducing ventilator synchrony—and cause considerable upset to family members. However, not all patients react similarly. Status myoclonus is defined as spontaneous multisegmental jerks persisting for greater than 30 minutes, most frequently accompanied by malignant EEG patterns (burst suppression or polyspike and wave patterns); prognosis in these cases is very poor. The clinical picture of myoclonus status cannot be missed. It is obvious and differs significantly from a few intermittent muscle jerks, which have no prognostic implications.

However, myoclonus status should not be confused with action myoclonus, also called *Lance–Adams syndrome*. The key distinguishing feature is severe myoclonus with motion or action and not at rest. The EEG shows a slowing background rhythm, which also differs from the frequent burst-suppression pattern in myoclonus status. In patients with action myoclonus, SSEPs, CT scans, and MRI scans are usually normal.[27–29] Although these myoclonic jerks can be very disabling (the patient cannot coordinate any movement stance or gait), they can often be reasonably well managed with oral levetiracetam, 1000 mg twice daily, in combination with valproate (maximum of 60 mg/kg/d); others have noted response to 5-hydroxytryptophan. Prolonged treatment is commonly necessary.

The clinical trajectory in comatose patients with anoxic–ischemic brain injury has been described. Recovery from coma usually occurs in stages: awakening, awareness, and communication. The time period can be short (ie, a couple of days) or protracted (a full week or longer particularly if patients have been sedated with long-acting drugs). These are patients in whom we cannot identify any clinical sign of severe injury. In contrast, patients who have already lost some brainstem reflexes and show early cerebral edema on CT scan may progress to brain death within days. Some may have been placed on ECMO as a last resort. One other category of clinical trajectory has been noted. These are patients who seem to improve but then have a secondary lapse into coma and demonstrate severe demyelinating disease. This *delayed anoxic encephalopathy* is exceedingly rare. (We cannot recall a sole case.) Typically, carbon monoxide or other gas inhalation provokes hypoxemia in these cases,[30] but opioid overdose can also provoke hypoxemia.[31] Hyperbaric treatment, suggested as a potential intervention, offers no proven benefit.

The neuropsychologic sequelae in survivors of cardiac arrest have been studied in detail. Approximately half the postresuscitation patients have severe cognitive deficits, and some have additional evidence of depression. Many recover over time, but patients with severe cognitive disability after postresuscitation encephalopathy often

show no improvement. Dramatic recovery from a severely disabled state after 1 month is rarely seen, and a 6 month outcome does not differ significantly from the outcome at the end of the first month.[32]

LABORATORY TESTS

Diagnostic tests that may assist in the neurologic examination include EEG, SSEPs, biochemical markers, computed tomography (CT), and MRI. The most common EEG finding is episodic low-amplitude events (ELAEs). ELAEs often correlate with medication effect and, therefore, do not suggest hypoxic–ischemic injury. When background EEG reveals generalized slow-wave pattern, the patient is more likely to have a better outcome. EEG, with faster frequency, spontaneous fluctuation, and reactivity to stimuli, may indicate the potential for neurologic recovery.[33] Conversely, a burst-suppression pattern or lack of reactivity on EEG often indicates a poor outcome.

SSEPs are a reliable prognostic tool; they are not confounded by medications, temperature, or metabolic factors. SSEPs stimulate the median nerve to elicit a potential at the brachial plexus, cervical spinal cord, and bilateral cortex potentials (N20). In order for the SSEP to be considered trustworthy, the cervical spine potential has to be acknowledged; this could be a possible concern in patients with severe anoxic–ischemic injury involving the cervical spinal cord. Moreover a short acting neuromuscular blocker may be needed to increase detection of the N20 and we have seen on several occasions these potentials to appear after its administration. The bilateral absence of cortical potentials (N20 component) on a reliable SSEP is nearly 100% definite in predicting poor outcomes when completed between day 1 and day 3 postcardiac arrest. Instead, the presence of cortical N20 responses does not ensure awakening from coma.[34]

Biochemical markers identified to detect cerebral damage postcardiac arrest include serum NSE, which is a gamma isomer of enolase found in the neurons. A 3 fold rise in NSE has predictive value. Serum NfL chain is a new, reliable, and highly sensitive predictor of poor neurologic outcome postcardiac arrest. An upward trend (as in NSE) might not be as important for outcome, as most abnormal values are already in the 500 to 1000 pg/mL range.[35]

Neuroimaging is needed in every patient. In approximately 5% of patients, cardiac arrest stems from a primary structural brain lesion such as aneurysmal subarachnoid hemorrhage, which changes the prognosis. Most CT scans after cardiac arrest are normal; however, additional scans over the following days may demonstrate changes. CT changes are related to widespread cerebral edema. Early edema may appear in patients found comatose followed by prolonged resuscitation (**Fig. 1**). Often, these patients have several additional clinical indicators of a poor neurologic outcome. MRI is more reliable in prognosticating and provides details such as diffuse cortical injury that may additionally involve bithalamic and putaminal injuries (**Fig. 2**). Normal MRIs do not necessarily indicate a better outcome; patients who remain in a persistent vegetative state or minimally conscious states may have normal MRI scans. Brain atrophy may present months following initial injury. When comatose patients with severe global ischemic injury on MRI (as shown in Figure 2) remain medically supported, repeat MRI will show liquefactive necrosis. [36]

We can conclude that SSEP, EEG, MRI, NSE, and NfL may all be used in a full assessment of prognosis. We may be able to prioritize these tests with EEG and SSEP and biomarkers first followed by MR imaging. Overall, a combination of MRI, SSEP, and EEG abnormalities may be the most helpful information for accurate prognostication. For example, the presence of electrographic “status epilepticus” or burst

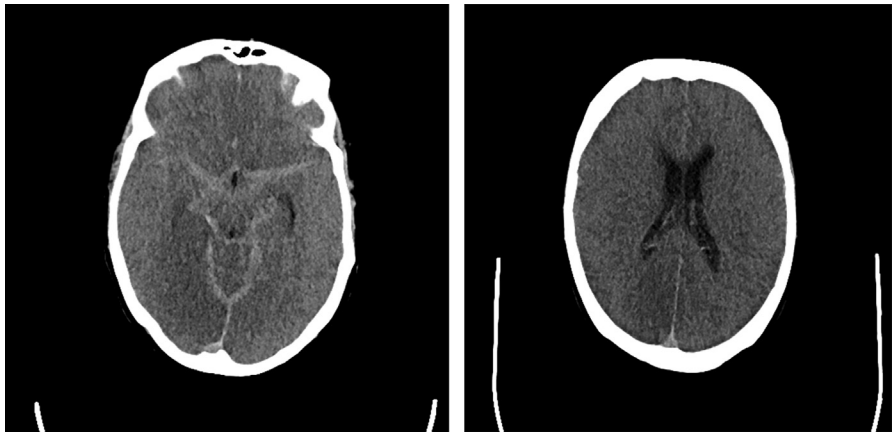

Fig. 1. Comatose patient following prolonged CPR. Note pseudo-subarachnoid hemorrhage, loss of sulcal architecture and hypodensities in the thalami and occipital parietal regions. This pattern on CT scan is not common but predictive and often associated with a poor neurologic examination (*left* and *right*).

suppression, absent N20 responses on SSEPs, and diffuse cortical injury on MRI strongly predict a poor outcome.

CONTROVERSIES

Two serious issues remain. The first is electrographic seizures.[37,38] A major conundrum is whether "electrographic status epilepticus" or other rhythmic patterns in comatose patients are potentially treatable. Periodic discharges and rhythmic patterns occurring at frequency of greater than 2.5 Hz, associated with spatiotemporal evolution and subtle ictal clinical accompaniments are often classified as seizures. A recent randomized trial for treatment of rhythmic and periodic activity after cardiopulmonary resuscitation (TELSTAR) randomly assigned patients either to antiepileptics in a protocol of escalating treatment to suppress all electrographic seizure-like activity or to no treatment. Both groups had similarly high mortality (80%, intervention group vs 82%, control group) and similar functional outcomes at 3 months in the few survivors. Overall, 90% in the intervention group had poor outcome (cerebral performance category score: 3–5, on a 0–5 scale with higher scores indicating more

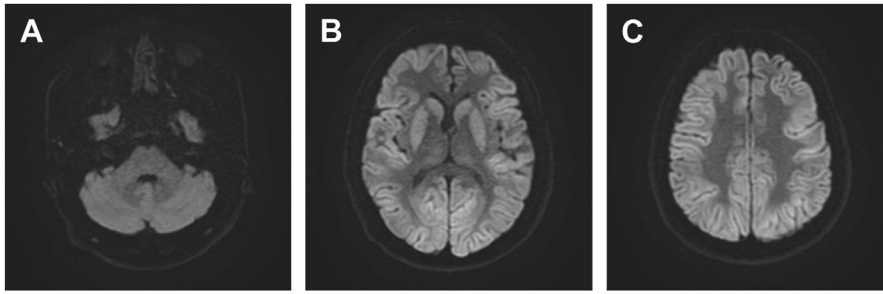

Fig. 2. MRI (DWI sequence) showing restricted diffusion in the entire cerebellar cortex, all of the (*A*) bihemispheric cortex, (*B*) caudate nuclei, and (*C*) globus pallidi. (*Adapted from* Wijdicks EFM. The Practice of Emergency and Critical Care Neurology [3ed]. New York: Oxford University Press, 2024.)

disability) compared with 92% in the control group. Serious adverse events were similar between the trial groups, indicative of the medical instability of these patients. ICU stays in the treated group were not extended by more than 1 day compared to the untreated group. This study strongly suggests that the treatment of these EEG abnormalities (reflecting significantly hypersynchronized, depolarizing neurons of the cortical mantle) does not affect outcome; indeed, the treatment of these EEG abnormalities may be futile (and possibly harmful). There are no evidence-based guidelines on how to treat patients in the ictal-interictal continuum patterns, and there is no consensus agreement on its definition.

The second issue is how to interpret brain edema on neuroimaging. The recent American Heart Association and Neurocritical Care Society statement surprisingly suggested placement of an ICP monitor.[39] This ignores the known fact that diffuse cerebral edema correlates with widespread cortical necrosis, including in the deeper structures, and is typically associated with a poor neurologic examination with absent brainstem reflexes—a situation more likely to occur in patients with nonshockable rhythms. The findings could be characterized as (1) diffuse mass effect with effacement of the cerebral sulci and of the brainstem cisterns; (2) global decrease in the cortical gray-matter density from edema, causing loss of the normal gray–white matter differentiation; and (3) low-density lesions of the basal ganglia bilaterally and decreased gray-matter density in watershed distributions bilaterally. (Subsequent contrast-enhanced scans can demonstrate selective enhancement of the cerebral cortex or the basal ganglia or both.) Yet, the interobserver reliability is likely poor, and brain edema might be misdiagnosed in young individuals with drug-induced respiratory and cardiac arrest and poor sulci architecture. Many patients with early, diffuse cerebral edema (CT scan with no characteristic features except diffuse gray/black) such as shown in **Fig. 1** will progress to clinical brain death, and repeat CT will show even worse effects with the loss of basal cisterns and tonsillar herniation.

CRITICISM

Over the years, neurologists have rejected their personal clinical experience (and relied on scientific facts. From time to time, we must acknowledge that the predicted outcome is indeterminate in more than half of the patients we see. We usually know who will do poorly, but we often cannot predict who will regain independence and full use of their intellectual capabilities. Guidelines and scientific statements are useful, but on the bases of these, an inexperienced clinician may aggressively use multiple antiseizure drugs with EEGs on the ictal and interictal spectrum, place an ICP monitor and treat marginally elevated values, being misguided by pupillometer changes rather than recognition of clinical patterns. Further, this clinician may postpone outcome determination out of the perceived fear that withdrawal of care may amount to self-fulfilling prophesy (**Box 1**).

Medicine is full of elusive numbers, and all the percentages can be dizzying. Number-based decision-making is significant and taxing. Moreover, statistics do not appear in a vacuum, and percentages have a so-called range, also known as the 95% confidence interval (CI). The 95% CI is a range of values for which we can be 95% confident that they reflect the true value of the population. For example, a 95% CI that the percentage of patients who will recover independent function is somewhere between 0% and 10% means that the chances are 1 in 20 that 10% of patients with this finding will achieve independent function. Some argue this is not certain enough. Even then, some family members may still be optimistic despite hearing the physician express serious doubt.

Box 1
Criticism of guidelines and scientific statements

- Lack of criteria for expertise in prognostication.
- Emphasis on EEG patterns and treatment of EEGs on the ictal-interictal continuum.
- Emphasis on pupillometry in sedated patients.
- Lack of definitions of abnormal clinical examination findings.
- Use of "likely" and "very likely" qualifiers in outcome determination.
- Consideration of placement of ICP monitor in brain edema.

Our consultation comes with duties. These are repeated examinations, documentation, communication, and compassionate end-of-life support. In most situations, we withdraw care when the family and the physician who most recently examined the comatose patient agree that no meaningful improvement is possible. In situations of disagreement, unwillingness, or denial, a member of a hospital ethics committee may provide advisory adjudication. An important goal of ethics is to preserve and

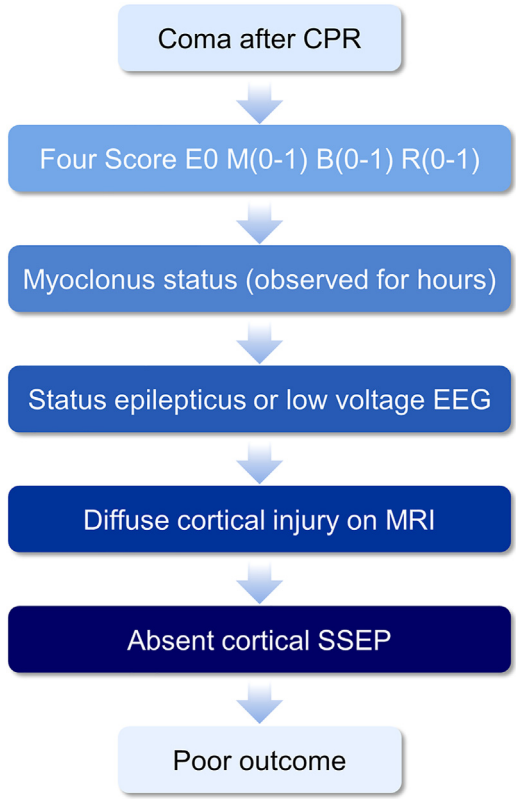
Coma after CPR
Four Score E0 M(0-1) B(0-1) R(0-1)
Myoclonus status (observed for hours)
Status epilepticus or low voltage EEG
Diffuse cortical injury on MRI
Absent cortical SSEP
Poor outcome

Fig. 3. Major clinical factors and tests results best predicting poor outcome. (*From* Wijdicks EFM. The Practice of Emergency and Critical Care Neurology [3ed]. New York: Oxford University Press, 2024.)

protect patient dignity. Ideally, that should override choices that conflict with autonomy. Information about a patient's clinical condition is the greatest universal need among family members, and we as physicians have a moral imperative to guard against common biases. Part of our medical and nonmedical decorum is to practice ethics to the fullest by recognizing pitfalls, biases, and wrong choices and working through them. We must explain what we do know (and do not know) with certainty, and we must address misconceptions. We have learned that improvement occurs most often seen in the first 3 to 7 days after a person becomes comatose. After that time, the chances become slimmer, although some patients do improve after longer periods of coma. Prior to placing tracheostomy and gastrostomy tubes, needed to facilitate long-term care, we must review an individual's history and test results before carefully considering which path to recommend to family members.[40,41]

SUMMARY

Of necessity, our priority is to identify poor prognosticators rather than good prognosticators (**Fig. 3**). Neurologists are seldom summoned to examine patients who seem lucid and may have luckily avoided a major injury to the brain. Failure to awaken is their cue for us to step in. We are not necessarily bearers of shocking news; we must also note indicators that the patient has a fighting chance to recover. We understand too well that recovery may depend on patients' pre-existing medical conditions and prior wishes—but also by what families are told about the patient's state and anticipated clinical course. We do that by recording the absence of poor prognosticators and appreciating that certain clinical or laboratory signs are inconclusive. We often find major confounders such as opioids or benzodiazepine infusions. Frequently, however, the news is not good—either the poor prognosticators are immediately obvious or the patient fails to show any signs of improvement. This raises the agonizing question of how best to proceed when all the clinical signs indicate a severe injury to the brain and organ systems. In those instances, it is our duty to have a compassionate conversation with the patient's loved ones to define goals of care.

DISCLOSURE

The author has nothing to disclose.

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Advances in the Critical Care of Ischemic Brain Infarction

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KEYWORDS

• Ischemic stroke • Thrombolysis • Endovascular treatment • Reperfusion

KEY POINTS

- Tenecteplase is a safe and effective option for intravenous thrombolysis, with higher rates of early large vessel occlusion (LVO) reperfusion and easier administration than alteplase.
- The indications for endovascular treatment (EVT) within 24 h of last known well are rapidly expanding after positive trials in large core and basilar artery occlusion strokes.
- The anesthetic management during EVT is still debated, with no clear superiority of general anesthesia over procedural sedation.
- Intensive blood pressure lowering after successful cerebral reperfusion of LVO strokes is harmful and should be avoided.

INTRODUCTION

Twenty years after the approval of intravenous thrombolysis (IVT) with alteplase for the treatment of acute ischemic stroke (AIS) several positive trials opened the era of endovascular treatment (EVT) for large vessel occlusion (LVO) strokes, changing the prognosis of this devastating condition.[1] Later, advanced brain imaging was introduced to select patients with salvageable brain tissue for EVT up to 24 h after symptom onset.[2,3] EVT is also beneficial in acute basilar artery occlusion (BAO),[4,5] and large ischemic core.[6] Tenecteplase (TNK) has been introduced as an effective option to alteplase, with the benefit of easier administration and higher rates or early recanalization in LVO strokes.[7] The periprocedural management of patients undergoing EVT, including head position, anesthetic management, and blood pressure lowering treatments has been refined, and the risk benefit equation for the early initiation of anticoagulation in patients with cardioembolic stroke better assessed. The complexity and fast evolution of this field requires a multidisciplinary team effort and continuous training in institution-specific stroke protocols. This paper aims to provide an updated and evidenced-based summary of the latest developments in the critical care of AIS.

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Neurol Clin 43 (2025) 91–106
https://doi.org/10.1016/j.ncl.2024.07.005 **neurologic.theclinics.com**
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Initial Evaluation: "Time is Brain."

Cerebral reperfusion treatments are more effective with earlier administration. The number necessary to treat (NNT) with IVT to help a patient achieve independence increases from 3.6 within 90 min of symptoms onset to 5.9 within 181 to 270 min.[8] Also, the odds of achieving lower disability at 90 d with EVT declines from 2.8 times when reperfusion occurs within 3 h to 1.6 times at 8 h.[9] Additionally, for every additional hour between admission and groin access, the odds of successful reperfusion decrease 22%.[10]

Intravenous Thrombolysis

Alteplase (0.9 mg/Kg) was the only safe and effective intravenous treatment for AIS until the introduction of TNK.[11] A lower dose of alteplase is not as effective as the standard dose.[12] TNK is a genetically modified variant of alteplase with 15 times more specificity for fibrin, 80 times less avidity for plasminogen activator inhibitor 1, and longer half-life (22 vs 4 min), which allows for a single bolus administration. Several randomized clinical trials (RCTs) have compared TNK with alteplase in different clinical scenarios (**Table 1**).[7,13–19] In some studies, TNK was associated with better clinical outcomes[7,19] and higher rates of early reperfusion in patients with LVO (22% vs 10%).[20] The standard TNK dose of 0.25 mg/Kg is superior to a lower dose (0.1 mg/Kg), and higher doses (0.4 mg/Kg) provide no additional benefit.[16,19] TNK is equivalent to alteplase for most indications, yet the one-time bolus administration and higher recanalization rates in LVO strokes make it a preferred option for drip and ship protocols.[21]

Nowadays, there are only a few absolute contraindications for IVT.[11] When symptoms are mild and improving the decision for IVT can be challenging. This is relevant because up to one-third of patients with mild symptoms who do not receive IVT remain disabled at 3 mo.[22] The best available evidence shows that patients with mild non-disabling symptoms treated with IVT have similar outcomes to those who receive antiplatelet therapy.[23,24] Although a low National Institute of Health Stroke Scale (NIHSS) (0–5) was a requisite for inclusion in the trials evaluating this question, the ultimate decision about the non-disabling nature of the symptoms was left at the discretion of the treating physician, underscoring the need for a tailored treatment approach for each patient.

IVT can also be considered when the time of symptoms onset is unknown in patients who have an ischemic lesion on diffusion-weighted MRI without FLAIR correlate. In the WAKE-UP trial, these patients were 60% more likely to have minimal or disability at 90 days when IVT was administered. There were no significant differences in the rate of symptomatic intracerebral hemorrhage (ICH) or death.[25] Yet, the study was prematurely terminated due to funding issues, with 503 out of the 800 anticipated patients included. Lastly, IVT with TNK (0.25 mg/Kg) was superior to no reperfusion treatment in patients with LVO presenting between 4.5 and 24 h from symptoms onset who had salvageable brain tissue identified on perfusion imaging but no access to EVT. Patients who received TNK had higher odds of modified Rankin Scale (mRS) 0 to 1 at 90 days (33.0% vs 24.2%), despite a higher rate of symptomatic ICH (3.0% vs 0.8%). Mortality was similar in both treatment groups.[26]

Mechanical Thrombectomy

EVT became the mainstay for the treatment of LVO strokes after the publication of the MR CLEAN trial in 2015.[2] In this study, EVT (in addition to IVT when indicated) was associated with higher functional independence at 90 d (32.6% vs 19.1%). More studies shortly followed, and regardless of differences in their inclusion criteria and

Table 1
Randomized Clinical trials comparing Alteplase with Tenecteplase in different clinical scenarios

Study, y, Sample Size	Phase, Intervention	Inclusion Criteria	Main Results
TAAIS, 2012, n = 75	2b, ATP (0.9 mg/Kg) vs TNK (0.1 or 0.25 mg/Kg)	<6h from onset, NIHSS >4, Age < 85 y, penumbra >20% than core on CTP and LVO on CTA	TNK had greater reperfusion and clinical improvement at 24 h No significant differences in intracranial bleeding and serious adverse events. TNK 0.25 mg/Kg superior to 0.1 mg/Kg
ATTEST, 2015, n = 104	2, ATP (0.9 mg/Kg) vs TNK (0.25 mg/Kg)	Patients eligible for IVT within 4.5 h of symptoms onset	No significant difference in penumbral salvaged, symptomatic ICH, or serious adverse evets
NOR-TEST, 2017, n = 1100	3, ATP (0.9 mg/Kg) vs TNK (0.4 mg/Kg)	AIS eligible for IVT within 4·5 h of symptom onset who were eligible for bridging therapy before EVT	Excellent outcome (mRS 0–1) achieved in 64% in TNK group and 63% in ATP group. Mortality and side effects similar in both groups
EXTEND-IA TNK, 2018, n = 202	2, ATP (0.9 mg/Kg) vs TNK (0.25 mg/Kg)	LVO AIS (including BAO) eligible to EVT within 4.5 h after symptom onset	Reperfusion >50% more frequent with TNK (22% vs 10% TNK had better 90-d functional outcome (median mRS, 2 vs 3) Symptomatic ICH in both groups
EXTEND-IA TNK 2, 2020, n = 300	2, TNK 0.25 vs 0.4 mg/Kg	LVO AIS (including BAO) eligible to EVT within 4.5 h after symptom onset	Reperfusion >50% 19.3% in both groups. No differences in clinical outcomes and side effects.
AcT, 2022, n = 1577	3, ATP (0.9 mg/Kg) vs TNK (0.25 mg/Kg)	AIS within 4.5 h of symptom onset eligible for IVT per guidelines	TNK non-inferior to ATP: mRS 0–1 at 90 d 36.9%, and 34·8%, and symptomatic ICH 3·4% and 3·2%, respectively
TRACE-2, 2023, n = 1417	3, ATP (0.9 mg/Kg) vs TNK (0.25 mg/Kg)	AIS within 4.5 h, baseline mRS <2 and NIHSS 5–25 eligible for IVT but ineligible for EVT	TNK non-inferior to ATP: mRS 0–1 at 90 d 62% with TNK and 58% with ATP. Symtomatic ICH 2% in both groups
TIMELESS, 2024, n = 458	3, TNK (0.25 mg/Kg) vs placebo	AIS with MCA or ICA occlusion and evidence of salvageable brain tissue on CTP (ischemic core <70 mL, penumbra/ core ratio $\geq$1.8, and penumbra $\geq$ 15 mL) between 4.5 and 24 h of LKW	No clinical benefit. Median mRS at 90 d 3 in each group. Symptomatic ICH 3.2% and 2.3% with TNK and placebo, respectively.

Abbreviations: AIS, acute ischemic stroke; ATP, alteplase; BAO, basilar artery occlusion; CT, computed tomography; CTA, CT angiography; CTP, CT perfusion; EVT, endovascular treatment; ICA, internal carotid artery; ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; LKW, last known well; LVO, large vessel occlusion; MCA, middle cerebral artery; mL, milliliters; NIHSS, national institute of health stroke scale; TNK, tenecteplase.

degree of clinical benefit, all confirmed the initial findings.[27] An individual patient-level data meta-analysis of these studies showed that EVT increased the odds of functional independence 2.5 times without increasing the risk of parenchymal hematoma and symptomatic intracranial hemorrhage (ICH).[27] The NNT to reduce disability by at least 1 point in the mRS was 2.6.[27] EVT remained effective in patients older than 80 y, those randomized beyond 5 h after symptoms onset, and those who were not eligible for IVT. The candidacy for EVT should not delay IVT when it is otherwise indicated because direct EVT failed to demonstrate its non-inferiority compared to IVT followed by EVT.[28] Additionally, IVT can achieve early recanalization in up to 20% of LVO cases,[16,20] it increases the odds of successful endovascular recanalization and may help treating distal embolization during EVT.

Endovascular Treatment in the Extended Window (6–24 hours)

EVT is beneficial up to 24 h of last known well in patients with salvageable brain tissue demonstrated by advanced brain imaging. The DEFUSE trial randomized patient with LVO, last known well 6 to 16 h before presentation and salvageable brain tissue assessed by computed tomography (CT) perfusion or MRI diffusion-weighted imaging (DWI)/perfusion to undergo EVT or receive best medical treatment (BMT). EVT increased the odds of 90-d functional independence (45% vs 17%) and showed a trend toward lower mortality (14% vs 26%). Symptomatic ICH (7% and 4%) and serious adverse events (43% and 53%) were similar in both groups.[3] The DAWN trial randomized patients between 6 and 24 h of last known well and a mismatch between clinical deficits (measured by the NIHSS) and ischemic core volume (assessed by DWI or CT perfusion). Again, EVT increased functional independence (mRS 0–3) at 90 d from 13% to 49%.[2] The rates of symptomatic ICH (6% vs 3%), and mortality (19% vs 18%) did not differ significantly between the treatment groups.[3]

Large Core Strokes

Large strokes pose a heightened risk of hemorrhagic conversion after cerebral reperfusion. Hence, patients with large ischemic cores were excluded from acute reperfusion trials. Six RCTs have recently tested the role of EVT in this population, defined as initial ASPECTS of 3 to 5.[6,29–33] These studies varied in their inclusion criteria and outcomes (**Table 2**). Most included patients up to 24 h from last known well, all showed the benefit of EVT in improving functional outcomes, and one (RESCUE-Japan-LIMIT) also suggested a mortality benefit.[31] The pooled analysis of these studies confirmed that EVT improves 90-d functional outcome (assessed by the mRS and utility-weighted mRS), the likelihood of functional independence and independent walking.[34] The rates of ICH were as high as 50% in patients who underwent EVT; however, cases of symptomatic ICH were not significantly higher.[34] Yet it is important to highlight that patients with severe strokes may not have a quantifiable increase in their severity scores despite having sizable hematomas with mass effect because the initial NIHSS is already in the higher end of the scale.

These results allow treating patients who would otherwise have a dismal prognosis and challenge the need for advanced brain imaging (MRI and CT perfusion) to select patients for EVT in the extended time window. In this direction, EVT has been beneficial in patients with AIS between 6 to 24 h of last known well when there is collateral flow in the middle cerebral artery territory of the affected hemisphere on CTA.[5] Similarly, the RESILINET-EXTEND trial randomized patients with NIHSS greater than or equal to 8 and high ASPECTS 5 to 10 to receive EVT or BMT. The preliminary results indicate that EVT was associated with better outcomes in people younger than 68 y, yet the publication of complete results is pending.[35] It is important to highlight that

Table 2
Large core stroke trials

Study, y, Sample Size	Intervention	Inclusion Criteria	Main Results
RESCUE-Japan-LIMIT 2022, n = 203	EVT + BMT vs BMT	18 y, NIHHS ≥6, mRS 0–1, M1 MCA or ICA occlusion, and ASPECTS 3–5. No FLAIR-MRI changes if randomized between 6–24 from LKW	mRS 0–3 at 90 d 31.0% with EVT + BMT vs 12.7% with BMT (RR, 2.43; 95% CI, 1.35–4.37). Improvement ≥8 points NIHSS at 48 h 31.0% EVT + BMT vs 8.8% with BMT (RR, 3.51; 95% CI, 1.76–7.00). ICH 58.0% and 31.4%, respectively. No differences in symptomatic ICH and death.
SELECT 2 (China), 2023, n = 352	EVT + BMT vs BMT	AIS within 24 h of LKW, 18–85 y, M1 MCA or carotid occlusion, ASPECTS 3–5, ischemic-core ≥ 50 mL on CTP or DWI-MRI.	Favorable shift in the distribution of mRS with EVT (OR 1.51 (95%, CI, 1.20–1.89). Functional independence 20% with EVT and 7% with BMT (RR, 2.97; 95% CI, 1.60–5.51). Mortality and sICH similar in both groups.
ANGEL-ASPECT (Australia, NA), 2023, n = 456	EVT + BMT vs BMT	AIS within 24 h of last known well, 18–80 y, NIHSS 6–30, mRS 0–1, M1 MCA or carotid occlusion. ASPECTS 3–5 no infarct-core volume limit. ASPECTS 0–2 based and infarct-core 70–100 mL. ASPECTS >5 between 6 and 24 h after stroke onset and an infarct-core 70–100 mL.	Stopped early due to efficacy of EVT. Favorable shift in the distribution of mRS (OR 1.37; 95% CI, 1.11–1.69; *P* = .004) at 90 d sICH 6.1% with EVT and 2.7% with BMT, any ICH 49.1% and 17.3%, respectively.
TENSION (Eu, Canada), 2023, n = 353	EVT + BMT vs BMT	AIS within 12 h of LKW, > 18 y, NIHSS <26, mRS 0–2, M1 MCA or ICA occlusion, ASPECTS 3–5 in CT or DWI-MRI.	Stopped early due to efficacy of EVT. Favorable shift in the distribution of mRS at 90 d (OR 2.58, 95% CI 1.60–4·.5) and with lower mortality (HR 0.67 95% CI 0.46–0.98) with EVT. sICH 6% wit EVT and 5% with BMT.
TESLA (US), 2024, n = 300	EVT + BMT vs BMT	AIS within 24 h LKW, 18–85 y, pre stroke mRS 0-, ICA or M1 occlusion, CT ASPECTS 2–5	90-d uw-mRS 2.93 ± 3.39 with EVT vs 2.27 ± 2.98 with BMT (adjusted difference, 0.63 95%CI -0·09, 1·34). 90-d mRS 0–3 30% with EVT vs 20% with BM (risk ratio, 1.50 [95%CI 1.00, 2.26]). Mortality (35%vs 33%) and sICH (4% vs 1.3%) were similar.
LASTE (Eu, US)	EVT + BMT vs BMT	AIS ≤6.5 h LKW or negative FAIR-MRI if unknown LKW. Age ≥18 y, pre stroke mRS 0–1. Intracranial ICA, M1, M1–M2 occlusion. ASPECTS 0–5 on CT or DWI-MRI, and ASPECTS 4–5 if ≥80 y.	Stopped early due to EVT benefit. Median 90-d mRS was 4 in the with EVT and 6 with BMT(OR , 1.63; 95% CI 1.29-2.06; P<0.001). Death at 90 days occurred in 36.1% with EVT and 55.5% with BMT (RR, 0.65; 95% CI, 0.50-0.84). Symptomatic ICH was 9.6% and 5.7%, respectively (aRR, 1.73; 95% CI, 0.78-4.68).

Abbreviations: AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT score; BMT, best medical treatment; CT, compute tomography; CTA, CT angiography; CTP, CT perfusion; DWI-MRI, diffusion-weighted magnetic resonance imaging; EVT, endovascular treatment; FLAIR, fluid attenuated inversion recovery; ICH, intracerebral hemorrhage; LKW, last known well; mL, milliliters; mRS, modified Rankin Scale; NIHSS, NIH stroke scale; sICH, symptomatic ICH; uw-mRS, utility-weighted mRS.

tomographic ASPECTS was created to evaluate early ischemic changes, not established brain infarction.[36] Furthermore, many large core trials assessed ischemic core with DWI-weighted MRI and excluded patients with matching FLAIR hypereintensity. These are key concepts because recanalization of established infarcts is unlikely to offer a clinical benefit and increases the risk of reperfusion injury and hemorrhagic conversion.

Basilar Artery Occlusion

BAO is associated with a grim prognosis if revascularization cannot be achieved. It usually has a subacute presentation with neurologic symptoms that are not well captured by the NIHSS, and non-contrast CT is inadequate for the evaluation of early ischemic changes in the posterior fossa. These characteristics challenge a rapid diagnosis, and explain, at least in part, the fact that these patients were systematically excluded from RCT for a long time.

After years of equivocal results,[37–40] 2 studies proved the efficacy and safety of EVT in patients with BAO up to 24 h after symptom onset.[4,5] In summary, EVT doubled the odds of 90-d functional independence, with an NNT to help 1 patient achieve a favorable outcome of 4 (**Table 3**). Although symptomatic ICH was numerically higher with EVT, these patients also had a trend toward lower mortality. These studies were performed in Chinese populations, who have a higher incidence of intracranial atheromatous diseases, yet a subgroup analysis from the ATTENTION trial showed a persistent benefit of EVT, regardless of the stroke etiology.[5]

Endovascular Treatment of Distal Occlusions

Between 25% and 40% of patients with AIS have distal medium vessel occlusions (MeVO).[41] Although IVT can resolve up to 50% of MeVO, medical treatment alone is still associated with significant disability.[41] Recent improvements of endovascular techniques and devices allow reaching distal arterial occlusions, making EVT an appealing option for MeVO, particularly for patients outside the treatment window for IVT. In a metanalysis of 2 RCT and 14 observational studies EVT was associated with better odds of functional independence, with no significant differences in symptomatic ICH, and mortality.[42] Three retrospective observational studies, 2 of them multicentric, showed that EVT is feasible and safe for the treatment of anterior circulation MeVO. In one of them (n = 138, 48 [34.8%] had EVT), patients who achieved successful reperfusion with EVT had a more pronounced improvement in the NIHSS upon discharge (5% vs 1%).[43] In another study (n = 286, 156 [54%] received EVT), EVT was associated with 70% higher odds of an excellent outcome (mRS scores, 0–1) at 3 mo.[44] The last one included 110 subjects with distal ACA occlusions (50% had EVT). Favorable functional outcome and mortality were similar in both groups.[45] Five ongoing RCTs are addressing this important clinical quandary (**Table 4**).[46–50]

Management Before and After Cerebral Reperfusion

Head of bed position

Collateral circulation supports brain tissue viability in AIS. Although transiently effective, avoiding hypotension and hypovolemia maintains collateral flow. Flattening the head of the bed increases cerebral blood flow and can augment collateral flow in AIS patients.[51] Although this was not beneficial in the Head Position in Stroke Trial,[52] the late administration of the treatment (the median interval from onset to treatment was 14 h), and inclusion of patients without LVO prevents from drawing definitive conclusions. The intervention was safe, and did not increase the rate of side effects,

Table 3
Latest clinical trials of endovascular treatment for basilar artery occlusion strokes

Study, y, Sample Size	Phase, Intervention	Inclusion Criteria	Main Results
BEST, 2019, n = 131	3, EVT + BMT vs BMT (including IVT)	BAO within 8 h of symptom onset	Terminated early (poor recruitment and high crossover). EVT not superior to BMT to achieve mRS 0–3 at 90 d in intention to treat analysis. EVT associated with better outcome (47% vs 24% in as treated analysis). Similar mortality. ICH more frequent with EVT (8% vs 0%, $P = .06$).
Basics, 2021, n = 300	3, EVT + BMT vs BMT (including IVT)	BAO within 6 h of symptom onset	EVT associated with non-statistically significant increase in favorable outcomes (44.2% vs 37.7%; risk ratio, 1.18 [95% CI, 0.92–1.50]). Symptomatic ICH more frequent with EVT (4.5% vs 0.7%).
ATTENTION, 2022, n = 340	3, EVT + BMT vs BMT (including IVT)	BAO within 12 h of symptoms onset, baseline mRS 0–2 (age <80 y) or 0 (age ≥80 y), NIHSS ≥10 pc-ASPECTS ≥6 (age <80 y) or ≥8 (≥80 y)	EVT improved the odds of mRS 0–3 at 90 d (46% vs 23%; risk ratio, 2.06 [95% CI, 1.46–2.91]). NNT 4. Lower mortality with EVT (36.7% vs 55.3%; risk ratio, 0.7 [95% CI, 0.5–0.8]). Symptomatic ICH 5% only with EVT.
BAOCHE, 2022, n = 217	3, EVT + BMT vs BMT (including IVT)	BAO or intracranial bilateral vertebral arteries occlusion within 6–24 h after symptom onset, age 18–80 y, prestroke NISHSS 0–1, NIHSS ≥6.	EVT associated with mRS 0–3 (46% vs 24% aRR 1.81; 95% CI, 1.26–2.60). Symptomatic ICH 6%. vs 1%

Abbreviations: BAO, basilar artery occlusion; EVT, endovascular treatment; BMT, best medical treatment; IVT, intravenous thrombolysis; NIHSS, NIH stroke scale; mRS, modified Rankin Scale; NNT, number needed to treat; ICH, intracerebral hemorrhage; pc-ASPECTS, posterior circulation ASPECTS.

Table 4
Median vessel occlusion strokes: ongoing randomized clinical trials

Trial, Estimated Sample Size	Inclusion Criteria	Endovascular Devices	Primary Outcome
DISCOUNT, n = 488	AIS ≤6 h of LKW, NIHSS≥5, isolated M2-M3, A1-A3, P1-P3 occlusion	Trevor, Preset, Catchview mini, and aspiration catheters	Dichotomized mRS (0–2 vs3-6) at 90 d
DISTAL, n = 526	AIS ≤24 h, NIHSS≥4 or disabling symptoms, M2-M4 occlusion and mismatch (FLAIR/DWI hypoperfusion/ hypodensity) between 6–24 h of LKW.	Any approved device	Ordinal shift of mRS at 90 d
DISTALS, n = 168	AIS ≤24 h, NIHSS 4–24, aphasia or hemianopsia, occluded artery diameter ≥1.5 mm, perfusion deficit ≥10 mL, core/penumbra ≤50%	Tigertriever 13	Successful reperfusion without ICH
ESCAPE-MeVO, n = 530	AIS ≤12 h, NIHSS≥5 or 3–5 with disabling symptoms, M2-M3, A2-A3, P2-P3 occlusion ASPECTS ≥6	Solitaire	Ordinal shift of mRS at 90 d
FRONTIER-AP, n = 240	AIS ≤9 h, NIHSS≥5 disabling symptoms, M2-M3, A1-A2, hypodensity of MCA or ACA territory <50% within 4.5 h or ischemic core <70 mL between 4.5–9 h.	Solitaire	mRS at 90 d

Abbreviations: AIS, acute ischemic stroke; ASPECTS, Alberta Stroke Program Early CT score; DWI-MRI, diffusion-weighted magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery; ICH, intracerebral hemorrhage; mL, milliliters; mRS, modified Rankin Scale; NIHSS, NIH stroke scale.

including aspiration pneumonia. In our experience lowering the head of the bed may be helpful as a bridging alternative in select patients with critical cerebral ischemia from proximal arterial occlusions. In this direction, the ZODIAC trial randomized 92 patients with hyperacute LVO strokes to 0-degree versus 30-degree head of bed positioning while waiting for EVT. In serial NIHSS examinations before EVT, patients in the 0-degree group were less likely to experience worsening of the NIHSS greater than or equal to 4 points. The lower NIHSS in the 0-degree group persisted 24 h and 7 d after randomization. Clinical outcomes at 3 m were similar in both groups.[53]

Anesthetic management during endovascular treatment

Whether patients undergoing EVT should receive general anesthesia (GA), or procedural sedation (PS) is debated in the literature. Proponents of GA claim the potential benefit of mitigating intraprocedural movements, increasing the chances of complete recanalization and reducing procedure related complications. On the other hand, GA can delay recanalization and compromise hemodynamic stability.

Initially, the analysis of 5 RCTs included in the HERMES collaboration suggested worse outcomes in patients with LVO strokes who underwent EVT under GA.[54] Subsequently, 7 RTC comparing GA with PS in patients with stroke from LVO treated with EVT showed no differences between the 2 anesthesia modalities.[55–61] A meta-analysis of the above-mentioned studies suggested improved recanalization rates and better clinical outcomes with GA. However, in this meta-analysis, the improvement in functional recovery depended on the removal of 2 studies in a sensitivity analysis.[62] In a multicenter cross-sectional study of 595 anterior circulation stroke cases from tandem LVO, GA was associated with less favorable functional outcome. There were no differences in symptomatic ICH, successful recanalization, excellent recanalization, first pass recanalization, early neurologic improvement and 90-day mortality. In a subgroup analysis PS was associated with better functional outcomes in patients younger than 70 years, NIHSS less than 15, and acute ICA stenting.[63]

Blood pressure management

Blood pressure maintains collateral flow, hence, it should not be treated before EVT unless it is extremely high or there is another outstanding reason. Once cerebral reperfusion is achieved, there is a theoretic concern that high blood pressure can worsen reperfusion injury, leading to ICH and poor clinical outcomes.[64] Initial observational studies suggested that systolic blood pressure less than140 mm Hg after successful cerebral reperfusion (TICI 2b-C) improved clinical outcomes.[65] However, 4 RCTs[66–69] warned about the opposite; patients who underwent blood pressure reduction using different targets had consistently worse clinical outcomes. A meta-analysis combining these studies showed that intensive systolic blood pressure reduction was associated with a lower likelihood of 90-day functional independence, excellent outcomes, favorable outcomes, and quality of life. There were no differences in the risk of any ICH, symptomatic ICH, stroke-related death, or parenchymal hematoma between the different blood pressure (BP)-target groups. Hence, systolic BP should not be lowered unless it is higher than 180 mm Hg, with new data suggesting that systolic blood pressure of 160 mm Hg may be the lower safety limit.[70]

Early initiation of oral anticoagulation

The main indication for anticoagulation in AIS is the finding of a major cardioembolic source, atrial fibrillation being the most frequent. The timing for initiation of anticoagulation depends on the risk benefit equation between prevention of early recurrences and avoidance of hemorrhagic complications. Based on the observation that

hemorrhagic transformation is related to infarct size, the "1-3-6-12–day rule" recommend initiation of anticoagulation at 1, 3, 6, or 12 days after a transient ischemic attack or after a minor, moderate, or severe ischemic stroke, respectively.[71] This clinical question has been addressed by 2 RCT. In the TIMING study, stroke patients were randomized to early (<5 days) or delayed (5–10 days) initiation of a direct oral anticoagulants (DOAC) within 72 h of stroke onset. Among 888 patients, early initiation was non-inferior to late initiation. There was a trend toward less stroke recurrence with early initiation and no patient in either group had symptomatic ICH.[72] The ELAN trial randomized patients with AIS to early (48 h after minor or moderate stroke and 6–7 d after a major stroke) versus late (3–4 d after a minor stroke, 6–7 d after a moderate stroke, and 12–14 after a major stroke) initiation of DOAC. There was a trend toward lower stroke recurrence in the early initiation group. Symptomatic ICH occurred in 0.2% in both groups. The incidence of a composite outcome that included recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic ICH, or vascular death ranged from 2.8 points lower to 0.5 points higher with early then late initiation of DOAC.[73] These data suggest that, although early initiation is safe, stroke size still matters, and should be considered in the decision-making process. Also, patients with indications for anticoagulation other than atrial fibrillation that carry a higher risk of early recurrence (eg, intraventricular thrombus, mechanical heart valves, etc.) were not included and may benefit more from an early anticoagulation. Two additional trials are ongoing to further clarify this problem.[74,75]

Decompressive hemicraniectomy

Malignant middle cerebral artery (MCA) stroke affects 10% of patients with hemispheric stroke and have a mortality rate of 80%. A comprehensive review on this topic can be found elsewhere.[76] The INTEP-AR score has been recently developed in a multicenter prospective study to identify patients more likely to develop this complication. The score includes stroke severity measured by the NIHSS, large infarct involving greater than or equal to 50% of the MCA territory, anterior cerebral artery (ACA) or posterior cerebral artery (PCA) involvement, pneumonia, and IVT and EVT as predisposing factors, and brain atrophy and arterial recanalization as protective ones. A score greater than or equal to 10 is the optimal cutoff for predicting the development of malignant MCA infarct (area under the curve 0.88, 0.82–0.95; sensitivity 0.84, 0.73–0.95).[77] When patients develop malignant swelling, several antiedema treatments can be used as temporizing measures, but decompressive hemicraniectomy is the only effective treatment. The clinical benefit of decompressive hemicraniectomy is clear for people younger than 60 y, with NNT to avoid 1 death and to achieve functional independence of 3 and 4, respectively. For patients older than 60 y, decompressive hemicraniectomy can be lifesaving but is rarely followed by recovery of independent ambulation.[78] Unlike the initial studies, an individual level patient data meta-analysis published in 2023 claimed a benefit of hemicraniectomy in people aged greater than or equal to 60. It also suggested a consistent benefit from hemicraniectomy regardless of hemispheric dominance and presence of aphasia.[79] These results should be interpreted with extreme caution because the meta-analysis included The Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery: a Randomized, Controlled Trial in a Turkish Population (DEMITUR). This RCT contributed with the largest sample size of people greater than or equal to 60, who also had significantly better outcomes compared to prior studies. Yet, it was withdrawn shortly after publication.[80] Also, outcome assessment with the mRS score does not fully address several quality-of-life domains or the impact of aphasia, underscoring the importance of a careful assessment on a case-by-case basis, considering

patients' preferences, and addressing the potential impact of individual symptoms in the long-term.[76]

SUMMARY

Reperfusion treatments for AIS have been expanded to a wide variety of clinical scenarios. Advances in endovascular techniques promise extension of EVT to patients with MeVO and the need for advanced brain imaging treatment selection is being revised. Careful monitoring in dedicated stroke units, timely initiation of secondary prevention treatment, and rehabilitation should follow cerebral reperfusion.

CLINICS CARE POINTS

- Patients with disabling symptoms from AIS should receive IVT with alteplase or TNK in the first 4.5 h of symptoms onset unless there is an absolute contraindication.
- In patients with non-disabling symptoms, antiplatelet therapy may be as effective as IVT.
- Patients with unknown time of symptoms onset are candidates for IVT if they have a DWI-MRI positive lesion without FLAIR correlate.
- IVT with TNK is a treatment option for patients with LVO and salvageable tissue in CT perfusion up to 24 h from symptoms onset when EVT is not available.
- EVT is the treatment of choice for patients with anterior and posterior circulation LVO up to 24 h after symptoms onset.
- Candidacy for EVT should not preclude IVT when otherwise indicated.
- Selected patients with ASPECTS score 3 to 5 are candidates for EVT.
- Keeping the head of the bed flat may help supporting collateral flow as a bridge for EVT.
- Intensive blood pressure lowering after cerebral reperfusion is harmful and should be avoided.

DISCLOSURE

The authors have nothing to disclose.

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High-Grade Subarachnoid Hemorrhage - Beyond Guidelines

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KEYWORDS

• Subarachnoid hemorrhage • ARDS • Intracranial hypertension • Vasospasm
• Delayed cerebral ischemia • Practice guidance

KEY POINTS

- Despite higher risk for complications and delayed cerebral ischemia (DCI), outcomes in high-grade subarachnnoid hemorrhage (SAH) patients can be favorable.
- Acute respiratory distress syndrome (ARDS) are common in high-grade SAH. ARDS management using higher positive end-expiratory pressure, lower tidal volume ventilation and prone positioning may affect intracranial pressure and cerebral perfusion pressure and require close monitoring.
- Angiographic vasospasm alone does not correlate well with cerebral infarction, DCI, or SAH outcome, and prophylactic treatment of asymptomatic vasospasm is not recommended.
- Prophylactic hemodynamic augmentation leads to complications without improving outcome and is not recommended.
- Symptom-driven treatment approaches for DCI commonly include hemodynamic augmentation and endovascular rescue therapies.

INTRODUCTION

Spontaneous subarachnoid hemorrhage (SAH), commonly caused by the rupture of an intracerebral aneurysm (85% of all cases of SAH), remains a life-threatening condition with high mortality and long-term morbidity. SAH patients present in a spectrum of clinical severity, commonly measured using the Hunt and Hess (HH) or the World Federation of Neurologic Societies (WFNS) score.[1] High-grade SAH is commonly defined as SAH patients who present with HH or WFNS scores of 4 or 5. These patients have significantly higher mortality and are at higher risk for SAH-associated complications, including delayed cerebral ischemia (DCI).

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Neurol Clin 43 (2025) 107–126
https://doi.org/10.1016/j.ncl.2024.07.006 **neurologic.theclinics.com**
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Although no novel therapeutics have improved SAH outcomes in clinical trials since the original nimodipine study in 1983, overall SAH survival and outcome are steadily improving over time. In-hospital mortality has decreased from 22.6% during 1985 - 1994 to 16.7% in 2005 - 2014, and the proportion of patients with good functional outcome at 6 months has increased from 64.8% to 78.8%.[2] Despite higher risk for morbidity and mortality, outcomes in high-grade SAH patients can be favorable.[3,4] This marks the critical nature in clinical decision making and critical care support of high-grade SAH patients, who experience many more severe complications. This article specifically examines the critical clinical scenarios commonly faced by high-grade SAH patients, including respiratory failure/acute respiratory distress syndrome (ARDS), severe DCI and cerebral vasospasm, and long-term outcomes beyond the modified Rankin score (mRS).

RESPIRATORY FAILURE AND ACUTE RESPIRATORY DISTRESS SYNDROME

Up to 38.5% of SAH patients experience acute respiratory failure requiring mechanical ventilation,[5,6] particularly high-grade SAH patients with reduced arousal. For SAH patients requiring mechanical ventilation, the 2023 American Heart and American Stroke Association (AHA/ASA) guideline recommends the use of the standardized ICU care bundle, which includes low tidal-volume ventilation, moderate positive end-expiratory pressure (PEEP), early enteral nutrition, standardized antibiotic therapy for hospital-acquired pneumonia, and a systematic approach to extubation.[5]

Common complications associated with acute respiratory failure include ventilator-associated pneumonia (VAP), and, in severe cases, acute respiratory distress syndrome (ARDS). A recent large randomized clinical trial (RCT) PROPHY-VAP examined brain-injured patients, including those with SAH, with Glasgow coma score (GCS) less than 12 and anticipated mechanical ventilation duration of more than 48 hours. In this population, 1 dose of prophylactic ceftriaxone reduced the incidence of VAP, mechanical ventilation duration, ICU length of stay, and mortality.[7]

ARDS occurs in up to 30% of SAH patients, with an incidence of up to 3.6% in the first 7 days after aneurysmal SAH,[8] with high-grade SAH patients are particularly at risk.[9] Developing ARDS with SAH is associated with worse functional outcomes and higher mortality.[9–13] Despite its high incidence and clinical impact, no RCT has specifically investigated optimal ARDS management in SAH.

Current evidence and recommendations from the American Thoracic Society guidelines support general management strategies for ARDS including using higher PEEP, limited tidal volume ventilation with permissive hypercapnia, prone positioning, neuromuscular blockade, glucocorticoids, and veno-venous extracorporeal membrane oxygenation (VV-ECMO).[5,14] There are limited data on the risk and benefit of these maneuvers in high-grade SAH patients who have concomitant high risk conditions such as cerebral edema and intracranial hypertension, which could be exacerbated by these maneuvers.[15] **Table 1** summarizes potential neurologic considerations of common ARDS management strategies in high-grade SAH patients.

Prone Positioning and Alveolar Recruitment Maneuvers

Prone positioning use in severe ARDS with hypoxemia can improve ventilation-perfusion matching and reduce lung compression, and is associated with improved survival in severe ARDS with arterial partial pressure of oxygen (Pa_{O_2}) to fraction of inspired oxygen (Fi_{O_2}) ratio less than 150 mm Hg.[16] However, prone positioning can

Table 1
Acute respiratory distress syndrome management strategies and potential neurologic impacts in high-grade subarachnnoid hemorrhage

ARDS Treatment Strategies per the 2024 American Thoracic Society (ATS) guidelines[14]	Potential Considerations in High-Grade SAH Patients
Higher PEEP without lung recruitment maneuvers	PEEP may increase ICP, particularly at higher levels recommend for ARDS therapy
Limit tidal volume (4–8 mL/kg predicted bodyweight) and inspiratory pressures (plateau pressure, 30 cm H_2O) and permissive hypercapnia	Hypercapnia may increase ICP
Prone positioning for 12 h per day in severe ARDS	• Prone positioning may increase ICP • Sedation needs may limit neurologic examination.[19]
Glucocorticoid use	Increased adverse events without clinical benefit in SAH
Neuromuscular blockers use with early severe ARDS	Neuromuscular blockade limits neurologic examination
VV-ECMO use in severe ARDS	• Systemic anticoagulation may be high risk in severe SAH, especially in patients with external ventricular drain (EVD) track hemorrhage or large areas of infarction • ECMO cannulation of internal jugular vein may reduce cerebral venous drainage and increase ICP

induce hemodynamic changes that impact cerebral blood flow (CBF). In patients with severe brain injury and cerebral edema at risk for intracranial hypertension, the cerebrovascular impact of prone positioning requires special consideration. Prone positioning can increase intrabdominal pressure. Data regarding the impact of increased intra-abdominal pressure on venous return and cardiac output is mixed, and the relationship may depend on factors such as intravascular volume status and preload responsiveness.[17–20] However, increased abdominal pressure can reduce cerebral venous outflow leading to intracranial pressure (ICP) increase, while simultaneously decreasing central venous return and lowering cardiac output, which in turn lowers the mean arterial pressure (MAP) and further reduces cerebral perfusion pressure (CPP). Head positioning associated with prone positioning may further impact cerebrovascular physiology and ICP by compressing neck veins, leading to decreased cerebral venous drainage and CBF.[21,22] Finally, body position and sedation required to achieve prone position can limit neurologic examination.[19]

Small RCTs and clinical case series provide data on prone positioning, ICP, CPP, cerebral oxygenation and cerebral perfusion in SAH patients (**Table 2**). While prone positioning clearly exerts physiologic effects on ICP and CPP, the changes may not be clinically significant and may not occur in every patient. The impact on CPP varies and may depend on adjuvant therapies to decrease ICP and increase MAP. A recent cohort study demonstrated that CPP and cerebral blood flow (measured by transcranial doppler) can be maintained even with increases in ICP during proning.[23] In exchange, prone positioning generally improves Pa_{O_2} and brain tissue oxygen (PbO2). Given the potential for ICP and CPP changes with prone positioning, monitoring of these parameters before and during prone positioning should be considered to ensure safety.

Table 2
Impact of prone positioning in subarachnnoid hemorrhage and severe brain injury

	Patient Population	Prone Duration	Neuro-Monitoring	ICP/CPP Treatment	Effects of Prone Positioning
Reinprecht et al[57] 2003	SAH (n = 16) with ARDS	$\geq$ 14 h	ICP & brain tissue oxygenation (IP probe)	EVD whenever possible; Mannitol, THAM, or hypertonic saline infusions administered for ICP >20 mm Hg	• Increased Pao_2 and PbO2 • Increase in ICP and decrease in CPP, not clinically significant • 2 patients turned to the supine position after 6 and 8 h because of ICP >25 mm Hg
Thelandersson et al,[58] 2006	SAH (n = 3), ICH (n = 2), and TBI (n = 6) with mechanical ventilation and $Fio_2 \geq 0.4$	$\leq$ 3 h	ICP (EVD)	EVD closed during procedure and not used for drainage	• Increase in Pao_2 and SaO2 • No significant changes in ICP or CPP • Prone position immediately for ICP > 20 mm Hg and CPP <60 mm Hg in 1 patient
Nekludov et al,[59] 2006	SAH(n = 2), ICH (n = 1), and TBI (n = 6) on mechanical ventilation	1 h	ICP (EVD)	Norepinephrine infusion to maintain CPP $\geq$ 60 mm Hg	• Increase in Pao_2 • Increase in ICP not clinically significant • Increase in CPP
Roth et al,[60] 2014	SAH (n = 15), ICH (n = 5), ischemic stroke (n = 1) and TBI (n = 8) patients with prone positioning because of respiratory failure	$\leq$ 8 h	ICP (EVD)	EVD as needed	• Increase in Pao_2/Fio_2 ratio • Increase in ICP not clinically significant • No significant decrease in CPP • Prone positioning replaced by continuous lateral rotational therapy because of elevated ICP in 3 patients

Bernon et al,[61] 2021	SAH (n = 11), ICH (n = 7), and TBI (n = 10) with ARDS	≤ 16 h	ICP and brain tissue oxygenation monitoring in 4 patients (method not specified)	EVD, craniectomy, hypothermia, osmotherapy, thiopental as needed	• Increase in Pao_2/Fio_2 ratio • Increase in ICP, sometimes clinically significant • Prone positioning discontinued because of sustained ICP elevation in 5 patients
Elmaleh et al[23] 2024	SAH (n = 4), ICH (n = 6), and other (n = 2) with ARDS	16 h	ICP & brain tissue oxygenation (intraparenchymal [IP] probe), CBF (estimated by TCD)	Vasopressor as needed to maintain CPP	• Increase in PbO2 and Pao_2/Fio_2 ratio • Increase in ICP • No significant decrease in CPP • No significant reduction of CBF

Abbreviations: ARDS, acute respiratory distress syndrome; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; EVD, external ventricular drain; Fio_2, fractional inspired oxygen; ICH, intracerebral hemorrhage; ICP, intracranial pressure; IP, intra-parenchymal; Pao_2, arterial partial pressure of oxygen; PbO2, brain tissue oxygen partial pressure; SaO2, arterial oxygen saturation; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TCD, transcranial doppler; THAM, tris-hydroxymethyl aminomethane.

Higher Positive End-Expiratory Pressure Without Lung Recruitment Maneuvers

The latest evidence suggests higher PEEP use without prolonged lung recruitment maneuvers (LRMs) in patients with moderate-to-severe ARDS is associated with impact on CBF, ICP, and CPP. Although data on the impact of PEEP on ICP are variable, there is concern that higher PEEP may be transmitted through the pleural space, elevate central and jugular venous pressure, and thereby increase ICP while simultaneously decreasing central venous return and reducing cardiac output, thus leading to reduced MAP, which may further lower CPP.[24,25] In brain-injured patients, elevated ICP may actually limit the transmission of PEEP to the intracranial compartment by compressing the cerebral venous system.[26] Additionally, reduced lung compliance in ARDS may minimize airway pressure transmission, thus reducing the possible impact of PEEP on MAP and ICP.[27] A recent study on PEEP changes in acute brain injury patients showed that PEEP changes did not result in clinically significant changes in ICP.[28]

Critical care support of SAH patients with ARDS demands a delicate balance to improve oxygenation while maintaining ICP control and cerebral perfusion. Some clinical studies in SAH suggest that PEEP of 20 mm Hg or greater may increase ICP and reduce MAP and CBF; however, vasopressors can restore MAP and normalize CBF despite sustained high PEEP (**Table 3**).[27,29] Of note, all studies of higher PEEP in SAH used concomitant ICP and CPP monitoring, which is prudent in this clinical scenario. There are limited data on the application of prolonged LRMs (eg, PEEP $\geq$ 35 cm H_20 for >60s) in SAH patients, and their use is no longer recommended.[14,30]

Corticosteroids

Corticosteroids are recommended in ARDS but not for the treatment of SAH-related inflammation, as metanalyses of observation and controlled clinical studies have shown increased adverse events such as hypokalemia, hyperglycemia, gastrointestinal bleeding, blood pressure changes, pulmonary embolus, and heart failure without significant changes in neurologic outcomes.[31,32] Given the benefit of corticosteroids in ARDS, corticosteroids should be considered in SAH patients with ARDS where mortality reduction may supersede the potential impact of adverse events.

Neuromuscular Blockade

Neuromuscular blockade use is recommended in severe ARDS, but it can impede serial neurologic examination in SAH patients. This should not preclude the use of neuromuscular blockage when indicated. In such instances, the addition of other neuromonitoring modalities to assess changes in neurologic status may be helpful.[15]

Venovenous Extracorporeal Membrane Oxygenation

ECMO is a potential rescue therapy in ARDS but presents unique challenges in patients with acute brain injury, such as SAH. The need for systemic anticoagulation with VV-ECMO should raise concern for recurrent intracranial bleeding, particularly in patients with craniotomy, intraparenchymal hemorrhage, large cerebral infarcts, or if the bleeding aneurysm has not been secured. Fluctuations in partial pressure of carbon dioxide ($Paco_2$) with VV-ECMO may directly impact CBF and ICP. Large cannulas in the internal jugular vein may obstruct cerebral venous outflow and raise ICP. Data on VV-ECMO in SAH patients with ARDS are limited to case reports but serve to address potential risks through protocol alterations such as avoiding continuous therapeutic anticoagulation and placing the ECMO return cannula in the left subclavian instead of the internal jugular vein.[33,34]

Table 3
Impact of positive end-expiratory pressure on intracranial pressure and cerebral perfusion pressure in severe brain injury and acute respiratory distress syndrome

	Patient Population	PEEP Levels	Neuro- Monitoring	Findings
Muench et al,[29] 2005	SAH (n = 10) requiring mechanical ventilation	PEEP up to 20 cm H_20 on days 1,3, and 7 after SAH with measurements of cerebral and hemodynamic markers 10 min after each incremental PEEP change	Thermal diffusion regional CBF probe Brain tissue oxygen probe	Only PEEP $\geq$20 cm H_2O resulted in a significant decrease in mean arterial pressure (MAP) and CBF, and higher ICP After MAP was restored with norepinephrine, CBF normalized despite the continued higher PEEP
Caricato et al,[27] 2005	aSAH (n = 11), severe TBI (n = 10) requiring mechanical ventilation	PEEP up to 12 cm H_2O, with measurements of cerebral and hemodynamic markers 15 min after each PEEP change Divided into patients with normal (>45 mL/cm H_2O) vs low lung compliance (<45 mL/cm H_2O)	ICP by EVD	No changes in ICP because of PEEP regardless of lung compliance group PEEP reduced MAP and CPP only in the normal lung compliance group

Acute respiratory distress syndrome impact on neurologic outcomes

ARDS in SAH patients is associated with increased duration of mechanical ventilation, longer ICU and hospital length of stay, higher mortality,[9–13] and worse functional outcomes as measured by the Glasgow Outcome Score (GOS) or mRS. There are currently no data on the impact of ARDS on cognitive function, quality of life, and other important patient-centered outcomes in SAH survivors.

Cerebral vasospasm and delayed cerebral ischemia

In addition to initial SAH severity and age, DCI is a leading cause of disability and unfavorable outcome in SAH, and one that is potentially reversible. This second phase of clinical deterioration may occur 3 to 10 days after the initial aneurysm rupture, and it may be associated with abnormal angiographic findings and/or new infarcts on computed tomography (CT) or MRI brain scan. The traditional hypothesis is that narrowing of cerebral arteries secondary to pathophysiologic mechanisms associated with SAH leads to reduced blood flow and decreased cerebral perfusion, and may result in ischemic infarction of the tissue distal to the arterial segments affected by vasospasm. Growing clinical evidence supports this being an overly simplistic concept. The association between angiographic findings, cerebral infarction, and clinical symptomatology is limited. In fact, up to one-third of patients with cerebral infarctions following SAH do not have corresponding angiographic findings in parent vessels.[35] Multiple large RCTs showed therapeutics that reduced or prevented angiographic cerebral vasospasm but did not improve patient outcomes.[1,36] Emerging science now suggests that ischemia from vasospasm is only one of multiple independent pathophysiologic mechanisms that contribute to secondary brain injury following SAH.[37]

Overlapping Terminologies

A myriad of variable and overlapping terminologies used interchangeably through the medical literature has added to the imprecision in the diagnoses of this second phase of brain injury after SAH:

- Angiographic cerebral vasospasm refers to constriction of cerebral arteries following SAH visible on digital subtraction cerebral angiography (DSA), cerebral CT angiography (CTA), brain MR angiography (MRA), or detected using transcranial Doppler ultrasound (TCDs) criteria. Anatomic studies, such as DSA, CTA, and MRA enable visualization of all major cerebral arteries and branches with variable resolution or more distal vessels. TCD detection of vasospasm is sensitive and specific for proximal vessels in the Circle of Willis such as the first segment of the middle cerebral artery (MCA), but less reliable in the posterior circulation, and does not visualize the anterior cerebral artery beyond the A1 segment.[38]In large SAH RCTs, vasospasm is often defined as reduction of cerebral artery diameter by more than two-thirds of its original caliber.[39] This terminology has also been applied to findings on cerebral CTA, although DSA remains the gold standard for vasospasm diagnosis. Patients with findings of angiographic cerebral vasospasm may or may not have clinically detectable neurologic symptoms.[40]
- Symptomatic cerebral vasospasm refers to new neurologic deterioration or persistent neurologic dysfunction attributable to ischemia in the vascular territory with angiographic cerebral vasospasm. In high-grade SAH, patients with altered levels of consciousness and/or requiring sedation for respiratory failure and ARDS, clinical detection of new neurologic deficits may be limited.

- Delayed ischemic neurologic deficit (DIND) is defined as at least a 2-point decrease on the modified GCS or an increase of at least 2 points on the abbreviated National Institute of Health stroke scale (NIHSS) lasting at least 2 hours.[39] This is an endpoint often used in SAH RCTs. To date, the most widely accepted definitions for DCI were published in 2010[41] and subsequently adopted through large consensus effort as common data elements (CDEs) in SAH in 2019.
- Clinical deterioration caused by DCI: focal neurologic impairment (such as hemiparesis, aphasia, apraxia, hemianopia or neglect) or a decrease of at least 2 points on the GCS lasting at least 1 hour, not immediately apparent after aneurysm occlusion, and cannot be attributed to other causes by clinical, radiographic, or laboratory investigations.
- Cerebral infarction caused by DCI: cerebral infarction on CT or MRI of the brain within 6 weeks of SAH or proven at autopsy, not present on CT or MRI between 24 and 48 hours after aneurysm occlusion.

Therapeutic Options for Vasospasm and Delayed Cerebral Ischemia

There is a large body of literature documenting a multitude of approaches and efforts to prevent and treat cerebral vasospasm and DCI. They can largely be separated into prophylactic treatments used before clinical deterioration or the diagnosis of DCI, versus symptoms-driven approaches.

Prophylactic treatments

Nimodipine. Enteral nimodipine use for 21 days following SAH is a high-level recommendation in the latest AHA/ASA and the Neurocritical Care Society (NCS) SAH guidelines (**Table 4**).[5,42] Nimodipine is often thought to work through prevention or treatment of vasospasm, which was not demonstrated in the original or subsequent studies. This assumption has at times erroneously led providers to discontinue nimodipine early and not complete the 21-day course established in the original RCT. Nimodipine can lead to hypotension, raising concern for CPP in vulnerable SAH patients with severe vasospasm and/or DCI, and nimodipine is often dose-reduced or stopped in these clinical scenarios. Although there are insufficient clinical data to determine the impact of total nimodipine dose on SAH outcomes, emerging pharmacogenomic studies suggest individual genetic variabilities in nimodipine metabolism significantly impact serum nimodipine levels, suggesting a future personalized medicine approach may be needed.[43]

Prophylactic agents previously tested in large phase III randomized controlled trials. Multiple potential therapeutic agents aimed at preventing or reducing cerebral vasospasm have been evaluated in large, multicenter phase III RCTs over several decades. These therapeutic agents include intravenous nicardipine (calcium channel antagonist), tirilazad mesylate (free radical scavenger), clazosentan (endothelin receptor antagonist), high-dose intravenous magnesium, oral simvastatin, and intraventricular extended-release nimodipine.[1] Although there was no increase in adverse events, none of these therapeutics met their primary end point of improving 90-day functional outcome compared with placebo. Of note, the clazosentan RCTs demonstrated that the drug reduced angiographic appearance of vasospasm but did not improve overall outcomes, further highlighting the potential discordance between angiographic vasospasm and SAH-related brain injury and outcomes.[44,45]

Targeting clinical deterioration caused by vasospasm/ delayed cerebral ischemia

Symptomatic vasospasm/DCI is common in high grade SAH patients. However, there are currently no high-level data to guide clinical management other than what not to

Table 4
Delayed cerebral ischemia prevention and treatment options: comparison of guidelines

DCI Treatment Option	AHA[5] Rec/Level of Evidence	NCC[42] Rec/Level of Evidence	Benefit	Caution
Nimodipine	Early initiation of enteral nimodipine (level 1A)	Recommend (strong; moderate quality)	Prevention of DCI, improve outcome	Hypotension
Endothelin antagonist	N/A	Against Lack of benefit on mortality or outcome and increase risk for AE (strong; high quality)		Pulmonary complications, fluid retention, anemia
Statins	Not recommended (3 no benefit, A)	Against. Lack of benefit (strong; high quality)	No benefit in DCI or mortality	
Magnesium	Not recommended (3 no benefit, A)	Against. Lack of benefit (strong; high quality)	No benefit in cerebral infarction or mortality	
Fluid administration	Maintain euvolemia is beneficial (2a, B-NR)	Target euvolemia, possible goal-directed hemodynamic therapy (conditional recommendation)	Potential increase in cerebral perfusion, reduce DCI, improve functional outcome	Liberal fluid use is associated with pulmonary edema
Blood pressure (BP) and cardiac output augmentation	In symptomatic vasospasm, elevate systolic BP may be reasonable (2b, B-NR)	Insufficient data, no recommendation	Potential increase in cerebral perfusion, reduce DCI, improve functional outcome	An underpowered RCT showed no improvement in functional outcome and more complications in induced hypertension arm.[46] Excessive induced hypertension may be associated with PRES.[62]

Prophylactic hemodynamic augmentation	Should not be performed (3 harm, B-R)	n/a	No benefit in outcome	Higher incidence of complications including congestive heart failure
Intra-arterial vasodilator	In severe vasospasm, IA vasodilator use may be reasonable (2b, B-NR)	N/A	Reverse cerebral vasospasm, reduce progression and severity of DCI	Systemic hypotension, elevated ICP during medication administration
Cerebral angioplasty	In severe vasospasm, angioplasty may be reasonable (2b, B-NR)	N/A	Reverse cerebral vasospasm, reduce progression and severity of DCI; greater durability in angiographic response compared with IA vasodilator	High mortality associated with vessel rupture

do. Both of the latest guidelines recommend against prophylactic hemodynamic augmentation because of a lack of clinical benefit and high incidence of complications.[5,42] In practice, the most commonly used therapeutic approaches for symptomatic vasospasm/DCI include

- Symptoms-driven augmentation of blood pressure and cardiac output to optimize cerebral perfusion
- Endovascular rescue therapies, including intra-arterial infusion of various vasodilators, most commonly calcium channel blockers, into the affected cerebral circulation and cerebral angioplasty of the vessels affected by vasospasm to restore cerebral perfusion

Existing guidelines offer differing guidance on these options, largely because of the limited level of clinical evidence. The only RCT that examined induced hypertension in DCI (HIMALAIA) was stopped early because of slow enrollment and was substantially underpowered to detect outcome differences. Although it did show 2.1-fold increase complications in the induced hypertension arm, baseline differences in SAH severity between the 2 arms preclude any reliable interpretation of the results.[46] **Table 4** summarizes major recommendations and differences in the latest AHA/ASA and NCS guidelines on vasospasm and DCI management in SAH, as well as potential clinical benefits and cautions with each therapeutic approach.

Refractory Vasospasm/Delayed Cerebral Ischemia – Beyond the Guidelines

One of the most challenging clinical scenarios in high-grade SAH patients is refractory vasospasm/DCI, where symptoms are recurrent, progressive, or persistent, despite first-line treatments. Without therapeutic intervention, these patients are at high risk for progressing to cerebral infarction, severe morbidity, and even death. However, potential additional therapeutic approaches in such clinical scenarios are experimental, high-risk, and supported by limited clinical data, generally from smaller retrospective studies or case series. Current clinical practice in severe vasospasm/DCI treatment is highly variable across regions, centers, and even individual partitioners,[47] further limiting the possibility of large, multicenter collaborative studies to generate the much-needed clinical evidence to establish risks, benefits, and patient selection criteria for these therapeutic approaches.

Table 5 summarizes some therapeutic approaches to severe vasospasm/DCI beyond existing guidelines, along with potential benefits and downsides based on the limited clinical evidence available. Intravenous milrinone infusion[48,49] induces cerebral vasodilation and increases cardiac inotropy; it has been studied in larger observational cohort studies of SAH and meta-analysis with relatively abundant data on risk profiles. The major adverse effect is systemic hypotension and higher need for vasopressor support. Repeated intraventricular nicardipine injections (most commonly 4 mg every 8–12 hours) through an external ventricular drain have been reported in smaller, retrospective studies with fewer data on potential adverse events and patient selection.[50] Prophylactic CSF drainage via lumbar drain has been studied in RCTs, with the latest, EARLYDRAIN, demonstrating efficacy on reducing cerebral infarction and improving SAH outcomes 6 months, although by a narrow margin.[14] This beneficial effect is not present on metanalyses combining all existing RCT data.[15] Percutaneous stellate ganglion blockade to reduce sympathetic outflow to cerebral arteries has been used to promote cerebral vasodilation in small RCTs that examined surrogate measures of brain injury with limited data on potential impact on SAH outcomes.

Given the limited evidence and high-risk scenario, treatment approaches to severe or refractory vasospasm and DCI may be best served with a multidisciplinary team

Table 5
Refractory vasospasm and delayed cerebral ischemia therapeutic approaches: beyond the guidelines

Therapeutic Approach	AHA[5] Reccommendations	NCC[42] Reccommendations	Mechanism and Potential Benefit	Caution
Intraventricular nicardipine injections[50]	N/A	None; insufficient data	• Direct cerebral arteriolar vasodilatation through circulation of drug into the intrathecal space • TCD velocities improved following injections, lasting for > 24 h	• Serial injections through EVD may increase infection risk. Overall reported rate is 6% • Small studies with limited data on safety, patient selection, complications
Milrinone intravenous infusion[48]	N/A; future research	N/A	• Increases cardiac inotropy, increase cardiac output • Cerebral vasodilatory effect through phosphodiesterase-III (PDE 3) inhibition • Large case series demonstrate drug is relatively well tolerated	• Vasodilatory effect on systemic circulation • Most common adverse event is hypotension (23%) and increase vasopressor support need • Hypokalemia occurs in 11% • May need adjustment for renal function
Prophylactic CSF drainage (lumbar drain)[63,64]	N/A; future research	N/A	• EARLYDRAIN RCT with lumbar drain for CSF diversion 5 mL/h starting within 72 h of SAH was associated with less cerebral infarctions at discharge and more favorable outcome at 6 mo	• 70% patients in lumbar drain group had an EVD • ICP gradient between cranial and lumbar drain pressures were monitored and lumbar drainage discontinued if the gradient is > 5 mm Hg • Prior RCTs, and meta-analysis including EARLYDRAIN, showed no effect on clinical outcome

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Table 5
(*continued*)

Therapeutic Approach	AHA[5] Reccommendations	NCC[42] Reccommendations	Mechanism and Potential Benefit	Caution
Neural ganglia block[65,66] (stellate ganglia block)	N/A; future research	n/a	• Percutaneous nerve block to reduce sympathetic outflow to cerebral arteries, potentially leading to cerebral vasodilation	• Potential complications include transient recurrent laryngeal nerve paralysis and voice changes • Limited data on impact on SAH outcome

approach and with shared decision making, particularly in areas where risks and benefits are not well established.

DISCUSSION

Outcome after SAH is evolving, and mortality and the mRS are insufficient measures to understand survivor experience and impact on individuals, families, and society. There are increasingly more SAH survivors,[51] including those who survived high-grade SAH. Even in patients who present with initial HH grade of 5, with modern surgical and critical care support, up to 39% achieve a favorable neurologic outcome and good cognitive function.[3,4,52] Despite the overall trend of improving survival and outcomes, significant variabilities in outcomes are seen across the United States and globally.[53] Although many factors may contribute to observed outcomes, existence of large SAH clinical care practice variabilities across individuals, centers, and regions is well documented.[47] There is evidence that protocolized, bundled care is associated with improved patient outcomes in larger population studies that include SAH patients, as discussed in recent published guidelines.[5] Published guidelines often do not address the most refractory and severe cases, as there are generally insufficient data and clinical evidence to support conclusive guidance. This article addresses some of the most common exceptions that are beyond existing guidelines.

Although SAH patients are surviving more and living longer, limited data on the quality of survivorship suggest many SAH survivors may continue to experience disability and altered quality of life many years after ictus.[54] Indeed, the number of people and number of years living with SAH-associated disability may be expanding. Emerging data, although scant, point to a significant burden of pain/headache, fatigue, PTSD, anxiety/depression, cognitive changes, hormonal dysfunction including sexual dysfunction, and social dependence/isolation, loss of work, and financial challenges in survivors.[55,56] There is even less information or clinical studies on potential therapeutic options to optimize quality of life, function, and overall wellness in SAH survivors. This represents an important knowledge gap in the care of SAH patients. The therapeutic course extends much beyond the acute phase of SAH and short-term ICU survival and a global functional outcome at 90 days.

SUMMARY

High-grade SAH patients are at high risk for severe disability and death, and yet favorable outcomes are possible, highlighting the importance of optimal critical care management in this patient population. Common severe complications include respiratory failure, ARDS, and severe cerebral vasospasm and DCI. There is limited randomized clinical trial evidence to guide management of these severe complications, other than the recommended use of enteral nimodipine to reduce DCI risk and improve SAH outcomes. ARDS management strategies in SAH patients require careful consideration of their potential impact on cerebral physiology including intracranial pressure and cerebral blood flow, which requires close monitoring and treatment. DCI remains an important and potentially reversible cause of morbidity and death particularly in high-grade SAH, but optimal treatment strategy for DCI remains controversial, and the current level of clinical evidence remains limited. Angiographic vasospasm has limited association with DCI and SAH outcome, and RCTs found therapeutic agents that reduced cerebral vasospasm did not improve SAH outcome. Prophylactic treatments to induce hemodynamic augmentation in patients with vasospasm but without clinical symptoms lead to high incidence of complications without outcome improvement and should therefore not be used.

CLINICS CARE POINTS

- Current ARDS management strategies such as higher PEEP, limited tidal volume, and prone positioning can improve systemic and cerebral tissue oxygenation but may also raise intracranial pressure, reduce cerebral perfusion, and lower cerebral venous outflow. ICP and CPP monitoring may be reasonable in these situations.
- Sedation and neuromuscular blockade use in ARDS limit clinical neurologic monitoring in SAH patients who are at high risk for DCI.
- Enteral nimodipine use can reduce DCI and improve SAH outcome, and it is a high-level recommendation in all existing SAH guidelines.
- Prophylactic hemodynamic augmentation in SAH leads to high incidence of medical complications without outcome benefit and is not recommended.
- Prophylactic use of endothelin antagonist, statins, and magnesium did not improve SAH outcome, and routine use is not recommended.
- Common treatment approaches to symptomatic vasospasm and DCI include hemodynamic augmentation and endovascular rescue therapies. Other potential treatment approaches, such as intraventricular nicardipine injections, milrinone intravenous infusions, prophylactic CSF drainage by lumbar drain, or stellate ganglia block remain experimental and have limited clinical efficacy and safety data.

DISCLOSURE

S. H-Y Chou reports compensation from CSL-Behring for consultant services; service as Board of Directors member for Neurocritical Care Society; compensation from Acasti Pharma for consultant services; research grants from the Neurocritical Care Society, United States; employment by Northwestern Medicine; employment by Northwestern University; research grants from National Institute of Neurological Disorders and Stroke, United States (R21-NS113037); and compensation from BioVie for consultant services. S. H-Y Chou serves on the editorial board for *Stroke* and serves as associate editor for *Translational Stroke Research*.

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Emergency Priorities in the Treatment of Cerebral Hemorrhage

Code-Intracerebral Hemorrhage

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KEYWORDS

• CODE ICH • Acute care bundles • Intracerebral hemorrhage • Neuroimaging • Blood pressure • Stroke • Hemorrhagic stroke

KEY POINTS

- Intracerebral hemorrhage carries high morbidity and mortality and is often undertreated.
- Ultra-early acute ICH care bundles, multiple therapies in parallel in the acute phase, appear to reduce morbidity and mortality in ICH.
- Proposed care bundle elements with time metrics include neuroimaging, blood pressure management, anti-coagulation reversal, hyperglycemia and hyperthermia prevention, surgical considerations, and cohorting.

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) accounts for 10% to 15% of strokes in the United States and has high morbidity and mortality rates. 40% of ICH patients die within 30 days and only a quarter have regained functional independence a year after hemorrhage.[1,2] Despite being extensively studied, therapeutic options proven in phase III randomized trials are sparse compared with those available for acute ischemic stroke (AIS). However, a wide body of observational evidence strongly suggests that specific interventions truly do change outcome, and 2023 saw the release of

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Neurol Clin 43 (2025) 127–139
https://doi.org/10.1016/j.ncl.2024.07.007 **neurologic.theclinics.com**
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multiple positive phase III randomized trials.[3–5] The focus of acute treatment of ICH includes prevention of secondary hematoma expansion, acute blood pressure management, timely reversal of anticoagulation, high-quality supportive care, and neurosurgical interventions for select patients.[2] Most recently, a wide range of evidence suggests that ultra-early acute ICH bundles, implementing multiple therapies in parallel, clearly reduce morbidity and mortality.[3,6] *Now is the time* for widespread implementation of formalized care bundles in ICH, including specific metrics for time to treatment and criteria for consideration of neurosurgical therapy. Now is the time to not just have "Code Stroke" but also "Code ICH"—with the goals of improving neurologic outcomes and establishing a platform for continued innovation, standardization of best practices, and ongoing quality improvement in ICH management.

Pathophysiology of Intracerebral Hemorrhage

The most common causes of primary ICH include hypertension and cerebral amyloid angiopathy, leading to rupture of small deep blood vessels within the parenchyma of the brain.[7,8] Secondary causes of ICH include arteriovenous malformations, cavernous malformations, deep venous anomalies, mycotic aneurysms due to infective endocarditis, hemorrhagic conversion of ischemic strokes, and tumors.[7,8]

In the first minutes to hours, primary brain injury occurs from the compressive effects of the hemorrhage itself. Total hematoma volume and amount of hematoma expansion (HE), the majority of which occurs within the first few hours of symptom onset, is a clinical predictor of poor outcome and is potentially modifiable making it an important target for timely therapeutic intervention.[9–12]

Secondary brain injury occurs as the inflammatory response is triggered by blood products within the parenchyma. This inflammation disrupts the blood brain barrier leading to perihematomal edema and tertiary injury by increasing intracranial pressure.[13–15]

Clinical Presentation and Diagnosis

Patients with ICH present with acute onset of focal neurologic symptoms and deficits related to the area of hemorrhage that can be difficult or impossible to differentiate from AIS until imaging is obtained. A rapid and focused evaluation includes establishing time of last known well, a physical examination focused on the airway, breathing, circulation, disability, and exposurealgorithm, and rapid neuroimaging. A non-contrast head computed tomography (CT) is the fastest and most convenient way to assess for the presence of blood. CT angiography has proved to be valuable to assess for contrast extravasation into the hematoma (ie, spot sign), which indicates an increased risk of ICH expansion, and to evaluate for underlying vascular abnormalities. Additional lab testing including coagulation studies and blood glucose levels should be routinely obtained.[8]

Initial Evaluation/Management

The care of ICH patients is critically time-sensitive with a focus on minimizing primary and secondary injury, which begins with preventing HE after initial hemorrhage occurs. Studies have demonstrated that approximately one-third of ICH patients experience HE within the first 3 hours of hemorrhage onset, and it is associated with worse outcomes.[9,11]

Risk factors for HE include hypertension and anticoagulation use. One critical goal is to minimize this risk of expansion. Another means of reducing final ICH volume is surgical evacuation, which likely improves outcomes for those who are candidates. Finally, while no single intervention has been shown to improve outcome in isolation,

a range of interventions appear to provide benefit when given in parallel, highlighting the critical role of good-quality protocolized care.

Blood pressure management

A primary cause of ICH is underlying hypertension, and high blood pressure (BP) on arrival seems to contribute to HE and poor outcomes.[16] Several trials have evaluated the effect of intensive BP reduction on outcomes.[17,18] While these trials failed to meet their primary outcome of a statistically significant difference in the modified Rankin Scale of patients who received intensive versus standard BP reduction, post-hoc analyses did show that early BP management was associated with a decrease in HE and improved outcomes.[18–20] Current American Heart Association /American Stroke Association guidelines recommend BP management be started as soon as possible, within the first hour of arrival, enacted in a smooth and sustained manner preferably with continuous antihypertensive infusion.[2] The recommended goal systolic blood pressure (SBP) is 130 to 150 mm Hg while avoiding drops in BP of >90 mm Hg especially within the first hour and then sustained for the next several days.[3] Reduction of SBP to <130 mm Hg in the acute phase should also be avoided as it can be harmful. Prehospital initiation of antihypertensive therapy may be beneficial in patients who have ICH, but implementation of this strategy requires availability of a mobile CT scanner because this early BP reduction may be instead detrimental in patients with ischemic stroke.[2]

Anticoagulation reversal

An important part of the initial history-gathering is determining anticoagulation status and time of last dose as reversal of anticoagulation, in addition to BP management, can decrease HE and improve outcomes.[2,21] Anticoagulation should be held and specific anti-reversal agents administered within the first hour of arrival, with an aspirational goal of door-to-needle (DTN) time of <30 minutes, as any benefit of reversal is likely time-dependent. Key components in expedited DTN time include rapid neuroimaging, intravenous (IV) placement, easy access to reversal agents, use of a simple pre-populated order set, elimination of time-consuming approval processes, and staff training in medication reconstitution and administration. Specific reversal guidelines include the following:

- *Vitamin K antagonists (VKAs)* can be rapidly reversed with Vitamin K and prothrombin complex concentrates (PCCs). This approach is recommended by the European Stroke Organization and the American Heart Association (refs); benefit is likely time-dependent.[22]
- *Direct oral anticoagulants (DOACs)* have become the most commonly used anticoagulants, and both specific and nonspecific reversal agents are available.[2,22]
  a. Factor II a inhibitors (dabigatran) should be reversed with idarucizumab, a monoclonal antibody fragment that binds dabigatran for hemostasis.[23,24]
  b. Factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban) should be reversed with andexanet alfa, a recombinant modified version of human Factor X. It binds Factor Xa inhibitors and appears effective for hemostasis in patients treated within 18 hours of last DOAC dose.[25] When andexanet alfa is not available, PCC should be administered instead. Preliminary data suggest that andexanet alfa may increase the risk of thrombotic complications, especially in those with prior history of AIS or myocardial infarction (MI) (**Fig. 1**).[16,25]

Temperature management

Hyperthermia is relatively common in ICH and is linked to early HE, neurologic deterioration, and poor outcome.[26,27] A post-hoc analysis of a large clinical trial found a

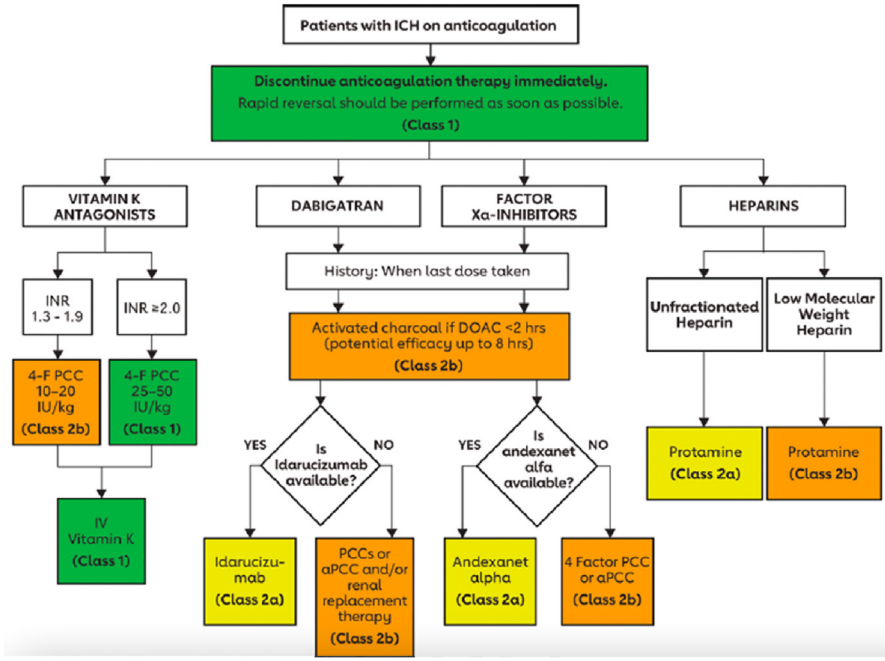

Fig. 1. Flowchart of anticoagulation reversal recommendations. (*Reprinted with permission* Stroke. 2022; 53: e282-e361. © 2022 American Heart Association, Inc.)

linear relationship between pyrexia and worse outcome even after adjusting for disease severity.[28] The QASC trial and the INTERACT-3 trial also found a benefit of temperature management. As a result of these and other studies, the AHA ICH guidelines recommend antipyretic treatment.[2,3,29] Another group specifically recommended the antipyrexia approach used in the INTERACT-3 trial: temperature checks every 4 hours with treatment of any temperature $\geq$37.5°C.[6] It is not clear that there is additional value in using a dedicated surface-based cooling system, as the recently completed INTREPID trial found no additional clinical benefit of using the Arctic Sun over standard care.[30]

Glucose management

Hyperglycemia is another common finding in many types of brain injury including ICH, even without a history of diabetes mellitus, and is associated with increased risk of HE, peri-hematoma edema, and worse outcomes.[31] INTERACT2, QASC, and INTERACT3 trials suggest that active management of hyperglycemia may reduce brain injury after stroke; however, there is a paucity of evidence-based guidelines for how best to enact this.[3,19,29] While awaiting further studies, the INTERACT3 approach may be the best for many centers:[6,32]

- Target blood glucose level of 6.1 to 7.8 mmol/L for nondiabetic patients
- Target blood glucose level of 7.8 to 10.0 mmol/L for diabetic patients
- Maintain this for up to 7 days or until hospital discharge.

Neurosurgical interventions

For select patients, early surgical therapy plays an important role in patient treatment.

External ventricular drain. Hydrocephalus is not uncommon after ICH due to obstruction of third or fourth ventricles by intraventricular blood or direct hematoma compression. Insertion of an external ventricular drain (EVD) is a common and relatively low-risk procedure which is considered lifesaving in acute hydrocephalus and is recommended by both AHA and European stroke organization (ESO) guidelines.[2,33]

Hematoma evacuation. Final ICH volume is a strong predictor of functional outcome.[1,34] Early neurosurgical hematoma evacuation reduces mass effect, lowers intracranial pressure, and lessens secondary injury, which may improve functional outcome. While many studies of open and minimally invasive hematoma evacuation failed to achieve their primary endpoints, they have shown consistent trends toward decreased mortality and improved outcomes.[35–37] The recent ENRICH trial and meta-analyses of older trials evaluating minimally invasive surgery suggest the greatest benefit with removal of most of the hematoma within the first 24 hours.[4,38] Ongoing trials will continue to contribute to the evidence base for minimally invasive surgery and allow for development of evidence-based consistent criteria for neurosurgical intervention.

Posterior fossa intracerebral hemorrhage. Cerebellar ICH carries increased risk of obstructive hydrocephalus or local mass effect on the brainstem due to the confined space within the posterior fossa. In practice, surgical management includes suboccipital decompressive craniectomy, hematoma evacuation, and EVD insertion with little experimental data to provide specific guidelines.[39]

Avoid early prognostication

Early prognostication has limited accuracy and can lead to "self-fulfilling prophesies" by which initial impressions lead to care limitations in cases with severe initial symptoms.[40–43] While it is important to respect the decision of patients and families to avoid futile treatment after a devastating illness with poor hope of meaningful recovery, this often relies on the assumption that the treating physician is able to accurately predict outcome in the specific case at hand. Evidence suggests that physicians tend to be overly pessimistic in early prognostication after ICH. Withdrawal of medical support and other early care limitations (like do-not-resuscitate (DNR) orders) within the first day of hospitalization are independent outcome predictors, even in those patients who do not actually have a cardiac arrest or require intubation.[40–42] AHA recommends that care limitations or withdrawal of support should not be recommended by treating physicians in the first 24-hours after ICH.[2,44]

BUNDLED CARE FOR INTRACEREBRAL HEMORRHAGE

While the afore-mentioned modalities are each independently important, the most impactful intervention in ICH management is the implementation of goal-directed care bundles—all therapies occurring in parallel. In the Quality in Acute Stroke care trial, uniform nursing protocols for fever, hyperglycemia, and swallowing dysfunction reduced disability and death at 90 days and 4-years post intervention.[45] In the Acute Bundle of Care for Intracerebral Hemorrhage study, bundling care including use of specific time targets for anticoagulation reversal and BP control and access to specialty resources in the acute phase of ICH reduced mortality.[5] In the INTERACT-3 trial, intensive BP lowering (target systolic BP <140 mm Hg), hyperglycemia and fever control, and reversal within 1-hour of arrival emergency department improved functional outcomes at 6 months.[3]

Bundled care across multiple domains of medicine has been shown to increase compliance with best practices and can improve performance and clinical outcomes.

Similar to how "Code Stroke" provides attentive, comprehensive, and uniform management of AIS and has shown real impact, implementation of "Code-ICH" shows promise as the future of the acute phase ICH management. By bundling care and enacting time metrics, ICH patients get the same focused attention in the early phase of the disease process (when it matters most) as AIS patients.

Standard Stroke Bundle Metrics

(Prompt assessment, history of present illness (HPI), and physical examination)
As in AIS, acute ICH management should include a rapid history-gather including history of trauma, anti-coagulation use (medication, dose, time of last dose, kidney function), and previous history of hemorrhagic or ischemic stroke.

(Door to computed tomography, goal $\leq$15 min)
When patients present with altered mental status or focal neurologic deficits, expedited imaging for diagnosis is critical and time sensitive. ICH and AIS can be difficult to differentiate until neuroimaging is obtained, rapid CT imaging can confirm the diagnosis of ICH as well as provide additional information about the hemorrhage.

(Door to lab results, goal $\leq$30 min)
Similar to AIS, rapid IV placement and laboratory studies (including international normalized ratio and other coagulation studies) should be obtained as quickly as possible to facilitate treatment.

Intracerebral Hemorrhage-Specific Metrics

(Door to needle, ie anticoagulation reversal, goal $\leq$30 min)
Time to anticoagulation reversal in ICH is critical.

A total of 20% to 40% of patients have HE within the first 3 hours of initial hemorrhage with the likelihood of HE increasing to 54% in anticoagulated patients. As such, early reversal maximizes the benefits, making this a critical, time-sensitive component of any ICH care bundle. While a goal of $\leq$30 min is aspirational, it provides a sense of urgency that is warranted to ensure reversal is achieved as quickly as possible.

(Door to first antihypertensive administration, goal $\leq$30 min)
Hypertension is a common finding in the acute phase of ICH and is associated with HE and poor clinical outcome.[46] Several lines of evidence suggest that achieving early and stable systolic BP reduction improves outcomes in patients with mild-to-moderately severe ICH. BP reduction should be initiated within 30 minutes of arrival and target SBP achieved within 60 minutes.[18,47]

(Door to blood pressure target, goal $\leq$60 min)
The beneficial effects of SBP reduction are likely time dependent. Studies have shown that average time to achieving BP control in ICH patients is well past the 3-hour HE window, thus providing an opportunity for improved quality of care.[48] While optimal SBP goals in acute ICH remain controversial, one good approach is as follows.

- Within 6 hour onset with initial SBP 150 to 220 mm Hg: aim for SBP <140 mm Hg
- For >6 hours, AHA guidelines recommend SBP target of 130 to 150 mm Hg and ESO guidelines target 110 to 140 mm Hg.

Additionally important is that target SBP should be achieved smoothly without fluctuations or large dips (>90 mm Hg) especially within the first hour. SBP control should be maintained for the next 7 days.[3,35]

(Door to hyperglycemia management—sustained euglycemia for the first 7 days)
Elevated blood glucose levels are relatively common in ICH and may worsen outcomes. While further studies are needed, a recommended approach (based off the INTERACT-3 trial) includes the following

- Target blood glucose level of 6.1 to 7.8 mmol/L for nondiabetic patients
- Target blood glucose level of 7.8 to 10 mmol/L for diabetic patients
- Sustained control for 7 days or hospital discharge

(Door to hyperthermia management—within 1-hour of measured fever)

Elevated temperature is relatively common in ICH and linked to poor outcome. ICH guidelines recommend antipyretic treatment. This can be implemented through every 4-hour temperature checks and treatment of any temperature $\geq$37.5°C.

(Door to neurosurgical, if done, earlier is better)
ICH volume predicts functional outcome thus neurosurgical management may be an important consideration in ICH care.[4] Hematoma evaluation may reduce mass effect, lower intracranial pressure, and lessen secondary injuries. Multiple studies including craniotomy for supratentorial trial, minimally invasive surgery with thrombolysis trial, and minimally invasive hematoma removal within 24 hours trial have shown benefit with early removal of most of hematoma volume.[4,36,37] Each institution should develop a neurosurgery consultation practice based on local experience and resources including evaluation for EVD or posterior fossa decompression for specific patients.

(Access to stroke unit or dedicated Neuro-intensive care unit)
AHA recommends that ICH patients be cared for in a dedicated neuroscience intensive care unit when available as this has been associated with a lower mortality rate (**Fig. 2**, **Tables 1** and **2**).[49]

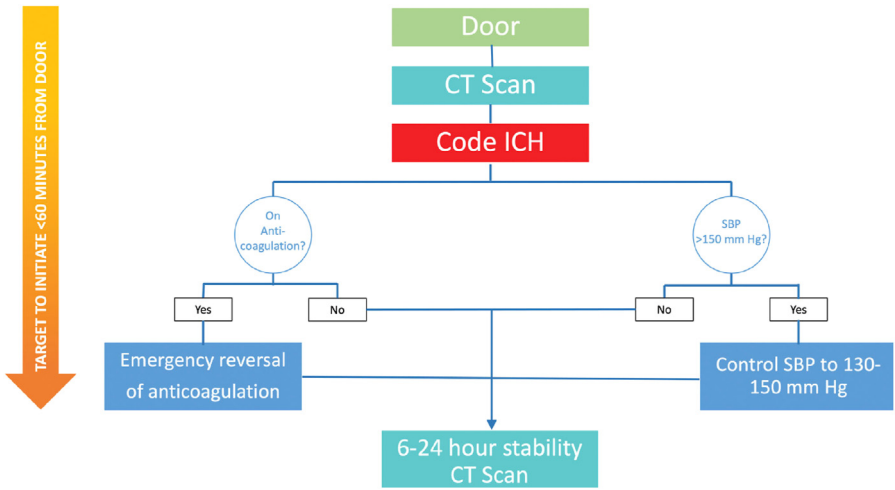

Fig. 2. Flowchart for 2023 code intracerebral hemorrhage workflow. The proposed door-to-needle target (initiation of treatment) for emergency reversal of anticoagulation and parenteral blood pressure control is 60 minutes. (Reprinted with permission from "CODE ICH: A Call to Action [Li et al, Ref.[32]].")

Table 1
Individual interventions for possible inclusion into an acute, intracerebral hemorrhage-specific bundle of care

Intervention	Criteria for Treatment	Recommended Process Targets	Supporting Guidelines/Key Evidence
Anticoagulant reversal	• PCC and VKA: (INR ≥1.3 • Andexanet alfa: currently taking apixaban or rivaroxaban and last dose taken ≤18 h • Idarucizumab: currently taking dabigatran • PCC (DOACs): taking a DOAC and specific reversal agent unavailable or unlicenced for specific agent	• Door-to needle time ≤30 min	1. ESO anticoagulant-associated ICH guideline (2019)[9] 2. AHA/ASA ICH guideline (2022)[5] 3. REVERSE-AD[12] 4. ANNEXA-4[13]
Intensive blood pressure reduction	≤6 h after symptom onset: SBP ≥150 mm Hg ≥6 h after symptom onset or unknown onset: uncertain, consider if SBP ≥150 mm Hg	• Treatment target ≤140 mm Hg, maintained for 7 d • Door-to-first antihypertensive: ≤30 min • Door-to-target: ≤60 min	1. ESO BP guideline (2021)[43] 2. AHA/ASA ICH guideline (2022)[5] 3. INTERACT2[44] & 3[3]
Surgical evacuation of Hematoma and/or external ventricular insertion	• Decision to operate on a case-by-case basis by multi-disciplinary team. Local criteria should be established to identify patients where a consultation with surgery must occur, for example,: • Patients with a pre-morbid mRS of ≤2, reasonable prognosis, and 1 or more of the following: 1. GCS ≤13 2. Supratentorial ICH volume ≥20 mL 3. Posterior fossa ICH 4. Obstruction of third and fourth ventricle(s)	• 100% of patients meeting consultation criteria are discussed with neurosurgery • ≤50% of patients not meeting consultation criteria are discussed with neurosurgery	1. ESO ICH guideline (2014)[29] 2. AHA/ASA ICH guideline (2022)[5]

Control of glucose	• Non-diabetic patients: Blood glucose >7.8 mmol/L in first 7 d • Diabetic patients: Blood glucose >10 mmol/L in first 7 d	• Non-diabetic patients: maintain blood glucose between 6.1 and 7.8 mmol/L for ≥90% of measurements in first 7 d • Diabetic patients: maintain blood glucose between 7.8 and 10 mmol/L for ≥90% of measurements in first 7 d • For both groups, optimize protocols to avoid hypoglycemia	1. INTERACT3[3] 2. QASC[33] 3. AHA/ASA guideline (2022)[5]
Control of temperature	• Monitor body temperature every 4 h for 7 d and initiate anti-pyretic treatment if temperature≥ 37.5°C	• Achieve normothermia (<37.5°C) within 1 h of starting treatment	1. INTERACT3[3] 2. QASC[33] 3. AHA/ASA guideline (2022)[5]

Abbreviations: AHA/ASA, American Heart Association/American Stroke Association; DOAC, direct oral anticoagulant; ESO, European Stroke Organization; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; mRS, modified Rankin Scale; PCC, prothrombin complex concentrate; SBP, systolic blood pressure; VKA, vitamin-K antagonist.

Adapted from "Acute care bundles should be used for patients with intracerebral haemorrhage: an expert consensus statement (Parry-Jones et al, Ref.[6])."

Table 2
Proposed time metrics created by a panel of experts for the 2022 Neurocritical Care Society Annual Meeting

National Joint Commission Ischemic Stroke Time Metrics		CODE ICH Proposed Hemorrhagic Stroke Time Metrics	
Door to Doc	≤10 min	Door to Doc	≤10 min
Door to Stroke Team	≤15 min	Door to Stroke Team	≤15 min
Door to CT scan start	≤25 min	Door to CT scan	≤25 min
Door to CT scan read	≤45 min	Door to CT scan read	≤45 min
Door to Needle (lytics)	≤60 min	Door to Needle (anticoagulant reversal)	≤60 min
Door to Arterial Puncture	≤90 min	Door to First Anti-hypertensive	≤60 min
		Door to Target Blood Pressure	≤90 min

Formal recommendations are pending further study.

Goldstein J, Frontera J, Alexandrov A, Kellner C, Yakhkind A, Mayer S. Code ICH. Oral presentation at NCS Annual Meeting. Oct 2022. Reprinted with permission from "CODE ICH: A Call to Action (Li et al, Ref.[32])."

CLINICS CARE POINTS

- *Pearl*: Intensive blood pressure management should be initiated quickly in a smooth and sustained manner with continuous infusion towards a set BP target.
- Expedited anticoagulation reversal relies on key orchestrated elements including rapid neuroimaging, IV placement, easy access to reversal agents, use of simple pre-populated order sets, and staff straining in medication reconstitution and administration.
- Initiate early consultation with neurosurgery as early surgical therapy/EVD placement is important for select patients.
- Goal directed care bundles/order sets can improve time to implementation of important acute ICH therapies as this can be a low frequency, high acuity event for many emergency departments/providers.

DISCLOSURE

Dr J.N. Goldstein has received consulting fees from AstraZeneca, CSL Behring, Octapharma, Takeda, Pfizer, NControl, Cayuga, and Prothya. Dr S.A. Mayer has received consulting fees from AstraZeneca. Dr M.M. Puissant has nothing to disclose.

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The Spectrum of Posterior Reversible Encephalopathy Syndrome

Jennifer E. Fugate, DO*

KEYWORDS

• PRES • Autoregulation • Seizure • Encephalopathy • Vasogenic edema

KEY POINTS

- Posterior reversible encephalopathy syndrome (PRES) is a clinical radiographic syndrome consisting of subacute symptoms with bilateral vasogenic edema on imaging.
- The ultimate underlying pathophysiology of PRES is thought to be endothelial dysfunction, either brought on by transmural pressure exceeding upper limit of autoregulation or a direct toxic effect.
- Some patients develop a severe form, "malignant PRES," which may require aggressive medical and surgical interventions in the intensive care unit.
- Most patients with PRES have favorable neurologic prognosis and do not require long-term antiseizure medication.

BACKGROUND

Posterior reversible encephalopathy syndrome (PRES) is a clinical syndrome consisting of acute to subacute neurologic symptoms in at-risk patients with characteristic brain imaging findings. In many cases, the diagnosis of PRES is forthcoming, such as when a confused or seizing patient presents with severely high blood pressure and has classic parieto-occipital vasogenic brain edema on brain MRI. It is well known, however, that PRES may present with a wide range of symptoms and that in some cases, MRI findings may be "atypical" (ie, edema involving less classical areas such as the brainstem or thalami).[1] While the majority of patients with PRES have both clinical and radiographic resolution, some patients have more permanent sequelae and rarely may even have a "malignant," or fatal form.[2–4]

The initial description of PRES is often attributed to Hinchey and colleagues in a case series of 15 patients from the early 1990s, referred to then as posterior leukoencephalopathy syndrome.[5] The term PRES was later coined in 2000.[6] Yet,

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Neurol Clin 43 (2025) 141–152
https://doi.org/10.1016/j.ncl.2024.07.008 **neurologic.theclinics.com**
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unsurprisingly to clinicians, reports of hypertensive encephalopathy date back nearly a century.[7] PRES classically occurs in the setting of severe arterial hypertension (ie, "hypertensive emergency"), but can also occur with marked blood pressure fluctuations. Many additional conditions have been associated with PRES including renal failure, sepsis, (pre) eclampsia, malignancy, cytotoxic drugs, and autoimmune disorders. We continue to learn about the boundaries of the ends of the PRES spectrum. Most of our understanding of the syndrome is derived from relatively small single- center retrospective observational studies.

ETIOLOGY

While knowledge of the precise etiology and pathophysiology of PRES is incomplete, endothelial dysfunction is widely believed to be the final common pathway that leads to PRES. There are various diseases and medication effects that can cause this. It has been long believed that hypertension and hyperperfusion are factors in a majority of patients with PRES. In normal physiology, cerebral blood flow (CBF) is autoregulated to remain relatively constant, despite changes in mean arterial pressure (MAP). One of the multiple underlying mechanisms of cerebrovascular autoregulation is vasoconstriction and vasodilation of brain arterioles in response to transmural pressure. Other factors that contribute to this adaptive mechanism include arterial carbon dioxide tension and the presence of vasoactive substances such as endothelin-1, thromboxane A2, and nitric oxide.[8] As MAP increases, arteriolar vasoconstriction occurs to maintain relatively constant CBF. Under severe hypertension, or a rapid, undulating increase in blood pressure, there is thought to be "breakthrough" of the upper limit of CBF autoregulation, resulting in endothelial injury and subsequent leakage of proteins and fluid into the brain interstitial tissue, causing vasogenic edema. This hyperperfusion theory is supported by the high proportion of PRES patients with high blood pressure or fluctuating blood pressure reported in the literature. It has been traditionally theorized that PRES predominantly affects the occipital and posterior parietal lobes because there are less autonomic receptors in the posterior circulation, leaving these regions potentially more susceptible to blood pressure changes.[9,10]

Severe hypertension and hyperperfusion seem to be sufficient but not necessary for the development in PRES. In fact, there are cases reported in which hypoperfusion (as defined by sequences from computed tomography [CT] perfusion scans) has been found in PRES, even with concomitant arterial hypertension.[11] Some theorize this could represent an overactive autoregulatory response to hypertension, but it is not well understood and needs further study. It is known that PRES can occur without hypertension, as reported in approximately 20% of cases, and in many of these circumstances, PRES is thought to result as a direct toxic effect on endothelial cells. This may be the predominant mechanism underlying PRES in sepsis, (pre)-eclampsia, autoimmune conditions, or in association with certain medications—particularly immunosuppressive and cytotoxic medications. The endothelium normally provides vascular integrity with a tight barrier made of cells connected by adhesion molecules. The presence of toxic substances or pro-inflammatory cytokines (for example, tumor necrosis factor alpha [TNFα], interleukin 1, and interferon-ϒ) may result in activation of endothelial cells, release of vasoactive agents, and increased vascular permeability, leading to interstitial edema (**Fig. 1**).[1] Vascular endothelial growth factor (VEGF) is one of the factors thought to be crucial in increasing vascular permeability and its expression is induced by TNFα. Concentrations of VEGF-A are increased in pre-eclampsia and eclampsia, which are strongly associated with PRES.[12]

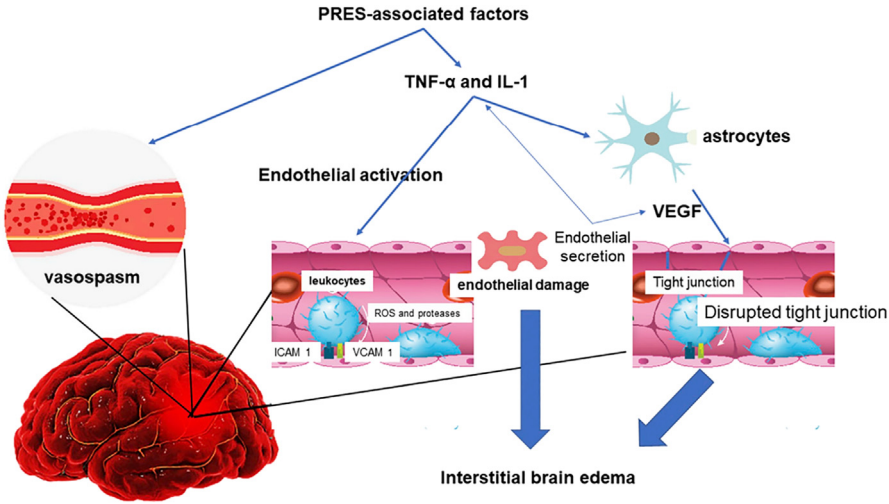

Fig. 1. Endothelial function and pathophysiology of posterior reversible encephalopathy syndrome (PRES). The release of cytokines TNF-α and IL-1 activates endothelial cells and increases expression of adhesion molecules ICAM-1 and VCAM-1 that leads to adhesion of leukocytes, endothelial damage, and fluid extravasation. TNF-α and IL-1 also can induce astrocytes to produce VEGF, weakening tight junctions and leading to increased vascular permeability. ICAM-1, intercellular adhesion mollecule 1; IL-1, interleukin-1; TNF-α, tumor necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1. (The figure has been adapted from Tetsuka S and Ogawa T. Posterior reversible enecphalopathy syndrome: A review with emphasis on neuroimaging characteristics. J Neurol Sci. 2019;404:72-79; with permission.)

CLINICAL PRESENTATION

Patients with PRES usually present with acute to subacute neurologic symptoms that have developed over the course of hours or several days. Occasionally, patients present with symptoms that have been ongoing for several weeks, but this is rare. The most common presenting symptoms of PRES are encephalopathy (reported in a wide range of 30%–90% of cases) and seizures (60%–75%). Encephalopathy can range from mild confusion to agitated delirium to coma. Seizures can be focal or generalized, and status epilepticus can occur. Bi-occipital epileptiform discharges in a confused or obtunded patient may be a clue to PRES.

Headaches, generally diffuse and gradual in onset, occur in up to half of patients,[13] though headaches and visual changes may be underreported because of concomitant presence of encephalopathy or seizures. A thunderclap headache should prompt consideration of a broad differential diagnosis, but does include reversible cerebral vasoconstriction syndrome (RCVS), which may coincide and overlap with PRES. Visual disturbances such as cortical blindness, hallucinations, reduced visual acuity, and visual field deficits are reported in up to 40%. Focal neurologic findings (eg, aphasia, hemiparesis) can be seen in 5% to 15%.

Because these symptoms of PRES are common in many neurologic disorders, it is crucial to correlate the clinical and radiologic findings in each individual patient to come to the diagnosis. While PRES has been traditionally defined as including both clinical and radiographic components, the borders of the syndrome continue to be explored and refined. While classic brain imaging findings make a diagnosis

straight-forward, there are also patients who present with symptoms suggestive of PRES that have normal head CT or brain MRI findings. Clinicians need to rule out other potential causes of the presenting symptoms, but once this has been done, an "imaging negative" PRES is a possibility. Conversely, in a retrospective study of patients with malignant hypertension, imaging findings of PRES were found in 16% of patients who had no neurologic symptoms at all.[14]

RADIOLOGIC FINDINGS

PRES is not strictly a radiological diagnosis; taking imaging findings in context with the clinical context is of upmost importance. Yet there are characteristic findings that can be seen, which include bilateral regions of subcortical T2 hyperintensity in the parieto-occipital lobes. While these regions of vasogenic edema may be seen on CT, MRI sequences are much more sensitive. The abnormalities are often asymmetric, but almost universally bilateral. Strictly unilateral signal abnormality is seen only very rarely (eg, in a patient with post carotid endarterectomy reperfusion) and this finding should generally make the clinician question the diagnosis. Classically, PRES involves the subcortical white matter, but often can involve the cortex as well.[1]

Three PRES patterns of brain involvement have been described in the radiologic literature. These patterns—a dominant parieto-occipital pattern, holohemispheric watershed pattern, and superior frontal sulcus pattern—may be found in up to 70% of patients.[15] Although not necessary to diagnose PRES, if seen, may be supportive for the diagnosis. There have not been consistent findings in the literature to support an association between radiologic patterns (or severity) of brain edema with specific clinical presentations, and the extent of brain edema on MRI does not correlate with the severity of symptoms.

In addition to the parieto-occipital lobe involvement (which is found to some degree in the vast majority of PRES patients), other brain regions are commonly affected. Vasogenic edema involves the frontal and temporal lobes in up to 70% to 75% of cases, the cerebellum in up to 50%, and the brainstem in about 25%.[10,16] While some refer to basal ganglia PRES as "atypical," this has been found in 12% to 34% of cases (**Fig. 2**).[10] Other less common regions of the central nervous system that have been involved in cases of PRES include the optic chiasm and the spinal cord.[17,18] Frequency of spinal cord involvement is likely underreported because most of the cases in the literature do not have symptoms referable to the spinal cord and thus spine imaging is not performed as often.

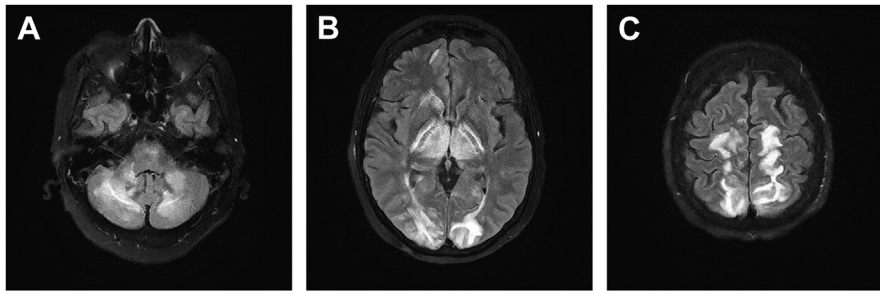

Fig. 2. Typical imaging abnormalities in PRES. Axial fluid-attenuated inversion recovery (FLAIR) MRI sequences show hyperintense T2 signal abnormality in PRES, including the bilateral cerebellar hemispheres and peduncles (*A*), parieto-occipital regions and "atypical" involvement of thalami and basal ganglia (*B*) and frontal watershed regions (*C*).

The presence of restricted diffusion or contrast enhancement is compatible with PRES. Diffusion-weighted imaging demonstrates restricted diffusion in about 20% to 30% of cases in most reports.[19] In several small series, it has been found to be associated with worse outcomes.[9,20] though in a small study, restricted diffusion abnormalities sometimes were reversible and not necessarily correlated with outcomes.[21] In general, regions of restricted diffusion in PRES consist of patchy, punctate, smaller areas that are much less extensive than the region of vasogenic edema.[22] (**Fig. 3**) Post-contrast enhancement is found in up to 20% to 25% of cases of PRES,[19] though no study has systemically addressed the timing of imaging in relation to symptoms and the prevalence of enhancement.

Intracranial hemorrhage complicates PRES in about 15% to 20% of patients and is usually located within or adjacent to regions of vasogenic edema.[23,24] This most commonly takes the form of intraparenchymal hemorrhage, followed in frequency by sulcal subarachnoid hemorrhage, though both forms can occur simultaneously.[25] Hemorrhages in PRES are more common in patients who are taking antithrombotics or have intrinsic coagulopathy, and in one study, in those undergoing allogenic

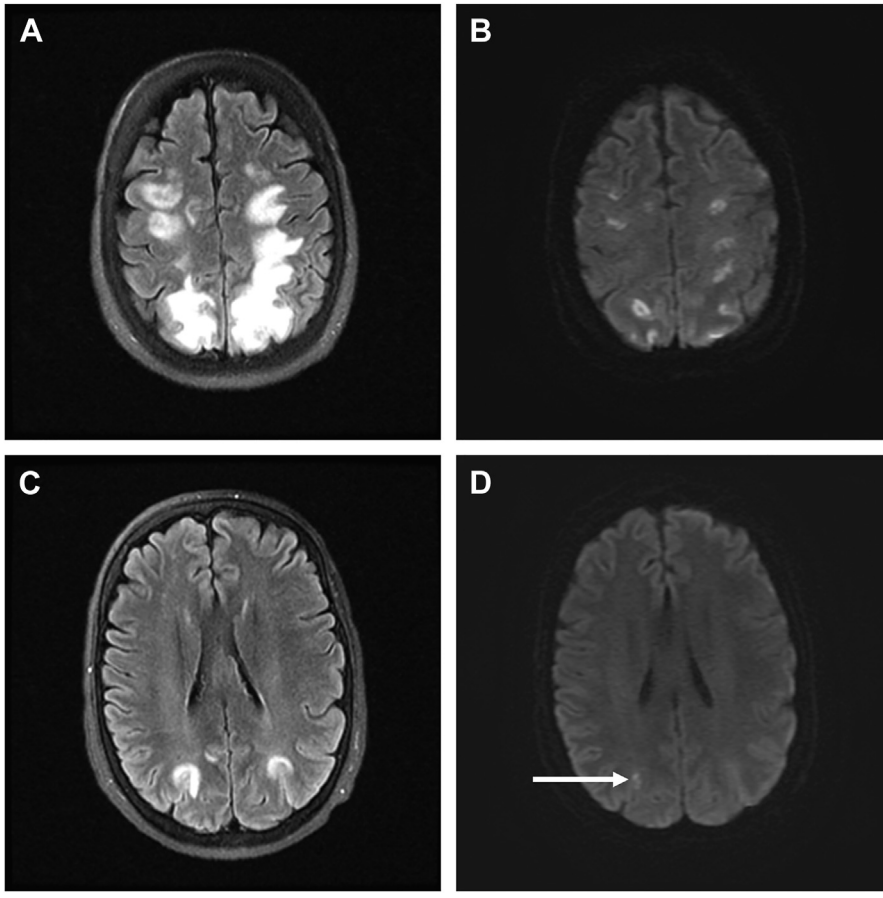

Fig. 3. Restricted diffusion in PRES. Axial FLAIR MRI shows characteristic T2 signal hyperintensity in bilateral hemispheres (*A, C*) and scattered cortical regions of restricted diffusion (*B*) and punctate region of restricted diffusion (*D, arrow*).

bone marrow transplantation.[24] Intracranial hemorrhage with mass effect has been associated with worse outcomes in PRES.[26] Microhemorrhages are commonly found on susceptibility weighted imaging sequences in MRI scans and are of uncertain clinical significance.

Vasoconstriction on vascular studies has been found in in PRES, though the prevalence is not well defined, as the literature consists mostly of single-center retrospective, observational studies. Reversible cerebral vasoconstriction syndrome is frequently associated with PRES and shares risk factors. While still controversial, it has been speculated that the 2 disorders may share a common pathophysiologic mechanism related to cerebrovascular endothelial dysfunction.[27] PRES has been reported in 9% to 38% of RCVS cases.[13] Patients with RCVS characteristically present with recurrent thunderclap headaches and on imaging have reversible multifocal vasoconstriction of intracranial arteries. Imaging findings may lag behind initial clinical presentation.

DISCUSSION

Management

The management of PRES depends on the underlying etiology. For those in hypertensive crisis or with marked blood pressure fluctuations, the mainstay of treatment is smooth and sustained reduction of blood pressure minimizing its variability. Typically, the goal in the treatment of severe hypertension is to reduce blood pressure by 25% within the first few hours followed by cautious normalization over the next 24 to 48 hours.[10] Seizures should be treated with antiseizure medications and any potentially triggering medication should be discontinued, at least temporarily. Failure to do so may result in prolonging of the syndrome.[28] Yet the optimal management strategy when there is a potentially causative medication that is temporarily discontinued is still unknown and there are some observational data that it may be safe to restart the offending agent. In a retrospective series in PRES patients taking tacrolimus, similar results were found whether the drug was restarted or the patient was switched to a different agent[29] and in another retrospective series, discontinuation of the potentially causative chemotherapy or hormonal medication, followed by reinitiation of the same drug did not lead to PRES recurrence.[30] Other associated disorders such as sepsis, (pre)eclampsia, and autoimmune disorders should be treated as per standard medical practice.

Outcomes

The prognosis for PRES is generally considered favorable, as the majority of patients will have both clinical and radiographic resolution. However, outcomes vary in the literature, as some investigators required proof of clinical and radiographic reversibility to be defined as PRES, and others did not. Those that do not require reversibility report complete recovery in about 75% to 90% of patients.[1,31] It takes a few days to a week on average to achieve full recovery. The presence of end-stage renal disease, malignancy, heart failure, stroke, and time to control the causative factor are clinical factors that have been associated with poor outcomes in PRES.[2,9,32,33] In a study utilizing the National Inpatient Sample for 635 patients hospitalized with PRES, 67% of patients were discharged home and overall mortality was 2.2%.[33]

While most patients have favorable prognosis, a subset of patients develop severe clinical presentations which can even result in death. Mortality rates are higher (5%–19%) in PRES patients who require admission to an intensive care unit (ICU).[32,34] Complications of posterior fossa edema with hydrocephalus and brainstem compression, intracranial hemorrhage, marked diffuse cerebral edema with increased

intracranial pressure are features that may characterize a "malignant" PRES (Fig. 4). There is no standard definition or set criteria for "malignant" PRES, but it has been described as "imaging studies in line with PRES; Glasgow Coma Scale less than 8; and continued deterioration despite standard management of raised intracranial pressure."[4] Early diagnosis is essential, as timely intervention may prevent an otherwise fatal condition. In a small case series of patients with malignant PRES, aggressive interventions, including intubation, hyperosmolar therapy, craniectomy, and hematoma evacuation led to a 0% fatality rate and no severe functional disability at 90 days.[4] At least 11 cases total have been reported in the literature for malignant PRES requiring decompressive hemi-craniectomy or suboccipital cranietctomy, 5 of which were associated with hemorrhage (Table 1).[4,35–40] Most of these patients recover favorably,

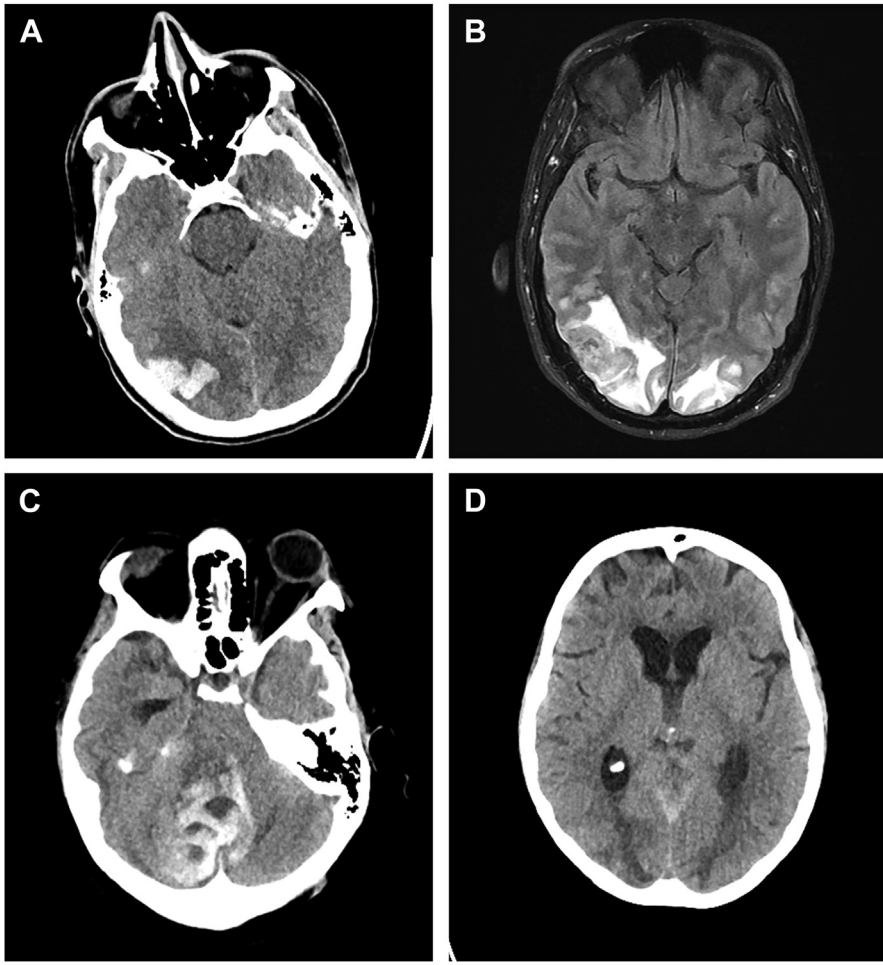

Fig. 4. Intracranial hemorrhage in PRES. (*A*) Axial computed tomography (CT) scan shows confluent region of intraparenchymal hemorrhage in right termporal-occpital region, which is located within a region of vasogenic brain edema seen on axial FLAIR MRI (*B*). Axial CT in a different patient shows acute posterior fossa intracranial hemorrhage with multiple fluid levels, mass effect, cistern effacement, and obstructive hydrocephalus (*C*). Characteristic occipital subcortical hypodensities indiciative of vasogenic edema were also present (*D*).

Table 1
Malignant posterior reversible encephalopathy syndrome requiring neurosurgical interventions

Age/ Sex	Reference	Clinical Presentation	Imaging—Edema Location	Imaging—ICH	Surgery	Outcome
32/F	Akins et al,[4] 2014	Seizures, hemiparesis, coma	Asymmetric hemispheric edema, brainstem edema	None	Craniectomy	mRS 2 (1 y)
29/F	Akins et al,[4] 2014	N/A	Diffuse edema	Occipital ICH	Hematoma evacuation, craniectomy	mRS 2 (1 y)
24/F	Akins et al,[4] 2014	N/A	Multifocal edema	Occipital ICH	Hematoma evacuation, craniectomy	mRS 1 (1 y)
29/F	Akins et al,[4] 2014	HA, vision, seizures	Diffuse edema	Occipital ICH, nonconfluent	Hematoma evacuation, craniectomy, EVD	mRS 1 (1 y)
50/F	Akins et al,[4] 2014	HA, vision, seizures	Bi-occipital vasogenic edema and diffuse edema	Occipital lobar ICH	Craniectomy, EVD	mRS 2 (1 y)
44/F	Hernandez-Duran et al,[40] 2019	Hypertensive emergency, left hemiparesis	Bi-frontal edema, corpus callosum	None	Craniectomy	mRS 2 (6 mo)
24/F	Katsevman et al,[36] 2019	HA, seizures	Bi-occipital edema, diffuse edema	None	Suboccipital craniectomy, VP shunt	mRS 1 (2 y)
39/F	Cossu et al,[35] 2019	HA, right hemiparesis	Asymmetric edema	Thalamic hematoma	Craniectomy	mRS 0 (3 mo)
52/M	Abusabha et al,[39] 2017	Hypertensive emergency, HA, vision	Edema in cerebellum, brainstem, occiput	None	EVD, Suboccipital craniectomy	mRS 0 (1 mo)
65/F	Grossbach et al,[37] 2014	Coma	Cerebellar edema	None	EVD, Suboccipital craniectomy	mRS 0 (6 mo)
47/F	Rodriguez et al,[38] 2023	Coma, DKA	Bi-parietal, occipital, frontal lobes, Basal ganglia	None	EVD, Craniectomy	mRS 6 (1 mo)

Abbreviations: EVD, external ventricular drain; F, female; HA, headache; ICH, intracranial hemorrhage; M, male; mRS, modified Rankin Score; N/A, not available.

and complete recovery has been reported, including in postpartum patients with eclampsia.[35] As the vasogenic edema does improve in natural disease progression of PRES (when triggers are treated appropriately), there has been a report of a patient in coma due to malignant PRES that improved without surgical decompression as well, though notably there was a lack of hemorrhage in this case.[41]

In regards to longer term outcomes, PRES can recur, particularly in patients with persistent risk factors such as suboptimally controlled hypertension, renal failure, or recurrent sickle cell crisis, but recurrences are not common. In small retrospective series, PRES was recurrent in about 4% to 5% of patients.[42,43] One study using the Nationwide Readmissions Database found that 31% of patients hospitalized because of PRES were readmitted within 90 days of discharge. The leading etiologies of readmission were infections (20%), hypertension (12%), renal or electrolyte issues (9%), gastrointestinal (7%), and PRES (6%).[44] Younger age, higher comorbidities, longer length of hospital stay, and discharge disposition to a place other than home were independently associated with the risk of readmission, while radiographic findings were not predictive.[44] Patients with PRES have a low risk of long-term unprovoked seizures, thus long-term antiseizure medications are generally not needed.[45]

SUMMARY

The boundaries of the spectrum of PRES, a clinical and radiographic syndrome, continue to be refined. In some cases, symptoms are mild and reverse within hours to days, and in others, severe and rapid neurologic deterioration demands aggressive medical and surgical interventions. A diagnosis of PRES requires clinical judgment as there is no 1 pathgonomic feature. Characteristic brain imaging findings consist of bilateral, often asymmetric, regions of subcortical vasogenic edema. Classically—and in the vast majority—this involves the parietal-occipital regions, but often also involves the frontal lobes, basal ganglia, and cerebellum. Intracranial hemorrhage (ICH) can occur with PRES; risk of ICH is increased in those with coagulopathy and its occurrence increases risk of unfavorable outcome. Most patients with PRES, however, have a favorable long-term neurologic prognosis and will have clinical and radiographic resolution with time.

CLINICS CARE POINTS

- Clinical presentations of PRES are nonspecific (seizures, encephalopathy, headache, visual disturbances) and usually develop over a day to several days.
- Brain imaging findings of subcortical vasogenic edema are often asymmetric but almost always bilateral.
- Restricted diffusion and contrast-enhancement are radiologic features consistent with PRES.
- "Malignant PRES" is associated with higher rates of mortality and may need aggressive ICU treatments including intubation, hyperosmolar therapy, and even neurosurgical decompression.
- The risk of long-term epilepsy in PRES is very low; the vast majority of patients do not need long-term antiseizure medication.

DISCLOSURE

The author has nothing to disclose.

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Advancing Neurocritical Care with Artificial Intelligence and Machine Learning

The Promise, Practicalities, and Pitfalls ahead

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KEYWORDS

• Artificial intelligence (AI) • Machine-learning (ML) • Neurocritical care • Neurology • Critical care • AI in medicine • AI and multimodal monitoring • Ethics

KEY POINTS

- Artificial intelligence (AI) is changing the paradigm of practice of medicine at a rapid pace and physicians and learners need to adapt to incorporate AI in clinical practice.
- Use of AI can expedite early diagnosis and intervention in acute neurologic disorders like stroke and intracranial hemorrhage and improve patient outcomes.
- Use of AI can potentially augment the realms of clinical diagnostics and management of patients in neurocritical care units with real-time multimodal monitoring.
- Emerging systems of multimodal AI–machine learning combine the use of text data, 2 dimensional imaging data, 3 dimensional biomedical (brain computed tomographic scan) data, and genomics or laboratory data.
- Regulatory and ethical frameworks for the use of AI in Medicine are emerging. Ethical implementation of AI systems in Medicine need to ensure transparency, safe applicability to diverse populations, accountability, and equitable access across health care systems.

INTRODUCTION

In the mid-twentieth century, the concept of mechanical brain or artificial intelligence (AI) was first formally explored outside the realm of fiction by scientists and mathematicians. Alan Turing, a British mathematician often cited as the father of modern AI, published

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Neurol Clin 43 (2025) 153–165
https://doi.org/10.1016/j.ncl.2024.08.003 **neurologic.theclinics.com**
0733-8619/25/© 2024 Elsevier Inc. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

the paper, "Computing Machinery and Intelligence" in 1950 to highlight the concept of developing learning machines to analyze and solve problems.[1] In 1956, John McCarthy and colleagues first coined the term "artificial intelligence" at the seminal conference on AI, the Dartmouth Summer Research Project on AI.[2] Machine learning (ML) is a practical application of AI where the statistical model learns from the dataset of existing knowledge and uses its experiential learning to identify patterns and make predictions on new data.[3] Deep learning (DL), a sin-branch of ML, has since capitalized on the advancements in computing processing units, such as graphical processing units and tensor processing units, as well as computational infrastructure, including high-performance computing and cloud computing. These resources enable DL models to handle vast amount of data, employing multiple layers of processing to automate the discovery of representations for feature detection or classification.[4]

Despite the progress in AI research and development, the public interest in this field ebbed and flowed with the period of its nadir often colloquially referred to as AI winter[2] which started in 1970s. During this period, there was a dearth of funding for research in this field, which led to deceleration in its growth and utilization. Notwithstanding these challenges, however, the advancement in AI-based technology continued and was reinvigorated in the twenty-first century to the point that it has now pervaded into every corner of modern life including transport, finance, education, defense as well as the field of medicine.

In 2011, Dr. Peter Densen highlighted the pace of increment of knowledge estimated by doubling time which is expected to be close to 70 days in 2020s as opposed to 50 years in mid-twentieth century.[5] In this age of rapid growth and super-specialization, the tasks of learning and medical practice have become encumbered across the board for the whole medical community. At the same time, the infiltration of AI in medicine offers new tools as well as challenges. At the precipice of this new age, physicians, students, and all practitioners have to face the challenge of adapting to incorporate this new paradigm into practice while maintaining the spirit and conscience of Medicine.

ARTIFICIAL INTELLIGENCE APPLICATION ON BIG DATA ANALYSIS

Most clinical studies are done on predefined subgroups of population with inclusion and exclusion criteria to answer a clinical question for that subgroup. The results from such studies are then extrapolated to similar subgroups, but the validity of such analysis is limited beyond those who lie within these defined characteristics. AI allows exploration of large volumes of existing data, without predefined delimiters for data visualization and analysis. Such analysis if done by human intelligence would be extremely slow and could end up in nonsolutions despite of scores of man hours investment. ML can argument this analytical power through the different models of dimension reduction (DR) where even nonlinear data with multiple dimensions or parameters are simplified while preserving the essence of the original data. The main approaches to this process are feature selection and feature extraction. Feature selection is a process where the most essential characters from the large dataset are retained while sacrificing the less critical data during the process of DR.[6,7] In contrast, the process of feature extraction creates new features within the existing dataset by combining the existing traits and thus preserving crucial information during the process of DR.[7]

Another application leveraging AI, specifically ML, on big data is clustering analysis. It is a powerful data exploration tool used to divide a multivariate dataset into natural clusters or groups with the goal of identifying underlying patterns and relationships

within the data. This can be used to identify correlations as well as anomalies or outliers within large datasets. Clustering analysis typically examines pairwise distances between objects to uncover intricate relationships. In contrast, DR or latent variable methods focus on the overall variance within the dataset, emphasizing broader gradients or patterns.[8] ML thus can be used to investigate large and complex clinical as well as biological datasets for exploration of endophenotypes and biodiscovery of molecules for various diseases.[9,10]

ARTIFICIAL INTELLIGENCE APPLICATIONS ON MEDICAL DATA

Due to the explosive growth of radiology and imaging based-diagnostics, the number of radiological examinations and number of images per examination have markedly increased in the last decade.[11] AI is transforming the field of radiology, often termed radiomics, by using algorithms to extract intricate features from the large database of medical images that may not be discernible to the human eye.[12] By analyzing texture, shape, and intensity patterns, radiomics enables us to uncover subtle abnormalities and patterns that contribute to more accurate diagnoses. These algorithms have been able to identify early and subtle signs of various diseases on imaging.[13] Computer vision is a field of AI that enables computers and systems to interpret visual information from digital images and other visual input using ML or DL to extract meaningful insights. It repeatedly analyzes vast amount of data until it can distinguish patterns and recognize images. Algorithms can be focused on organ systems and pathologies to detect specific findings pertinent to individual disease with high accuracy. AI-driven medical imaging analyses can perform at the level of radiologists.[14,15] Although most current models are still derived from small datasets and have limited external validity, the promise of computer vision is propitious.[16] Similar success has been achieved in other fields utilizing visual imaging including pathology,[17,18] ophthalomology,[19,20] and cardiac echocardiography.[21,22]

Natural language processing (NLP), similar to computer vision, is another field of AI that delves into the realm of linguistics.[23] It can create an interface between the user and the computer which harkens beyond the rules of traditional written text. NLP explores the vast domain of natural language as complex syntactic and phonological data.[23,24] This has a wide range of utility in clinical practice. Several different voice-to-text products are now widely available that utilize medical terminology in speech recognition and work as scribes dictating notes directly into the electronic health records (EHR) in real time allowing immediate review and editing. Using AI, these platforms can train themselves to profile individual users. It can even be used to respond to patients' queries where it has been found to be empathetic and of reasonable quality in one study.[25] Large language models (LLMs), leveraged by the generative AI, can be used to pre-populate notes based on the conversation from the clinical encounter, thus augmenting clinical care. The rising challenges in health care expansion, shortage of employees, and the addition of administrative roles on top of clinical duties has produced work–life imbalance and increased burnout among health care providers. A trained automated system that can assist in writing notes, and filtering, navigating, and responding to patients e-inquires may alleviate the stress and clerical burden of health care personnel. All these factors may lead to better health care and mitigation of physician burnout.

NLP can also be used for data-mining large volumes of unstructured text data such as clinical notes and scientific literature, thus serving as a helpful tool in clinical research.[26–28] NLP can also be used to assist clinical practice. It has been shown to

be a predictive tool for hospital admission from emergency rooms (ER) and can therefore be used to augment triage process in ER.[29,30] Machine-based language translation is rapidly evolving and may soon allow the development of a universal translation system to aid clinical practice beyond the confines of language barriers.[31]

AI–ML EXAMPLES OUTSIDE HEALTH CARE THAT CAN BE ASSIMILATED INTO HEALTH CARE

Recommender Systems

Numerous examples of AI–ML recommender systems exist in other industries (eCommerce). For example, Amazon and Netflix utilize recommender systems to use data in your product history or during your search to cross-match potential products based on other users (user to user match) or among similar products among other users. The application of recommender systems is powerful since it can help find a product quickly based on vast amounts of existing data from similar users and their preferences. Over time this process becomes more individualized. Currently, there are informatics examples in electronic medical records, such as providing suggestions when prescribing a medication, but these are not the same as recommender systems. For example, in the future AI could recommend certain treatments or medications for a patient with certain symptoms and signs based on comparisons with other similar patients.

Prediction

ML methods, especially Bayesian systems, can make inferences in probabilities of conditions which can help guide difficult diagnoses and avoid human anchoring bias toward one particular diagnosis. Simplistic logistic regression "calculators" are well recognized in neurocritical care such as the ICH score which provides a probability of mortality based on existing ICH patient risk factors. The number and quality of prediction models in neurocritical care, however, could improve over time with larger datasets.

Classification

Classifiers or recognizers are machine learning methods that recognize patterns in data. These can be text or data based, and more recently involved use of neuroimaging data such as large vessel occlusion recognition on computed tomography angiography (CTA), and calculating the area of penumbral brain tissue at risk. Classifiers can also be phenotypic as well as laboratory marker-based classification based on labeled or annotated data to train and validate ML datasets.

IMPORTANCE OF ARTIFICIAL INTELLIGENCE IN ADVANCING NEUROLOGIC CARE

With the aging population in the United States, the burden of neurologic diseases is expected to increase exponentially.[32] There is also an overall paucity of neurologists around the country with marked geographic variations, which will likely be exacerbated over the coming decades.[32–34] This warrants new and innovative solutions to prevent overburdening the system. Leveraging AI assistants could potentially alleviate this crisis to a certain degree. The principal role of AI assistants in Medicine is not to supplant physicians, nurses, and other health care professionals, but rather to address existing gaps in access to health care and research. Support in clinical care might encompass tasks such as pre-populating and transcribing notes, responding to patient inquiries, facilitating language translation during interactions, and even conducting literature reviews for complex cases.

ARTIFICIAL INTELLIGENCE IN NEUROCRITICAL CARE

The horizons for care of neurologic disorders, especially in the intensive care unit (ICU), are ever expanding and this is continued to improve patient care. There is marked heterogeneity in neuro-ICU patients even with similar clinical diagnoses and management should ideally be individualized to patients' needs within the parameters of guidelines and institutional protocols. This heterogeneity along with advances in neurologic care pose a great challenge to diagnosis, monitoring, and treatment of these patients (**Fig. 1**). The promise of AI to enhance the practice of neurocritical care is enormous, but just emerging.

Application of radiomics features extracted by AI algorithms has proven beneficial in several neurologic disorders such as dementia and central nervous system (CNS) malignancies.[35–37] Use of AI-aided radiological imaging has revolutionized stroke care by rapid analysis of salvageable ischemic penumbra on perfusion imaging that has been employed to extend the time window for mechanical thrombectomy.[38–41] AI-based computer-aided diagnostic tools are also streamlining the early diagnosis of different forms of intracranial hemorrhages such as intracerebral hemorrhage and subarachnoid hemorrhage and their complications such as cerebral vasospasm and risk of aneurysmal rupture.[42–46] Early diagnosis and timely intervention are crucial in neurocritical care to salvage brain tissue at risk of injury and harnessing the power of AI can expedite this process by saving valuable minutes and thereby millions of neurons.

Programs for automated seizure detection have existed since 1980.[47] However, their use in the clinical setting underwent a paradigm change with the use of artificial neural networks along with quantitative electroencephalogram (EEG) analysis with color-coded rhythmicity and fast Fourier transformed power spectrograms.[48,49] Although automated seizure detection products need supervision before its analysis

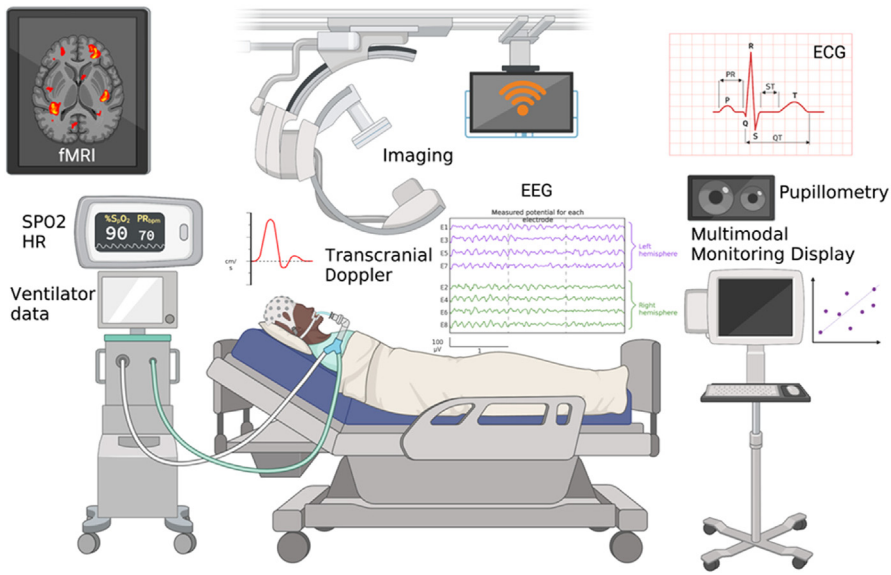

Fig. 1. Current state of multimodal monitoring (MMM) data in the neuroscience intensive care units (NSICU), which currently is all separate and hard to time-sync and label without an MMM platform to make scientific inferences. (Created in BioRender. Freeman, W. (2024) BioRender.com/j01m158.)

can be deemed actionable, their interpretation alongside a trained interpreter has proven to be a reliable tool for early seizure detection.[50–52]

Development of digital twins models using AI can create a virtual or digital parallel of a real-world system, allowing modeling of neuro-ICUs and testing of hypotheses in a virtual world.[53] The interplay between the extensive multimodal data from neuro-ICU patients including temperature, blood pressure, heart rate, intracranial pressure, ventilatory parameters, real-time fluid balance, neurologic examination, and modalities like EEG, transcranial Doppler, near-infrared spectroscopy, brain blood flow, and tissue oxygenation monitors and so forth can be obscure and difficult to interpret. Using AI systems can allow real-time analysis of multimodal inputs to allow for increased diagnostic accuracy and timely interventions to improve outcomes (**Fig. 2**).[54] It can also be used to compile and mine biological data from vital signs, EHR, medical imaging, changes in clinical parameters based on diurnal rhythms and medication administration to aid in multimodal monitoring, and development of newer modalities of treatment.

AI-based LLMs have proven adept at reviewing existing literature.[55] This does not always transcribe into tackling clinical situations but can definitely aid in syndromic analysis of rare disorders (syndrome sniffer) based on data from clinical encounters. Incorporating AI assistants in clinical care may even help mitigate anchoring biases in patient care.[56] It has also been utilized for telemedicine, tele-neurology, and tele-critical care. It can assist in the process of triage, screening, and monitoring of patients and can aid streamlining the tele-workflow.[57–59] In the field of tele-robotics,

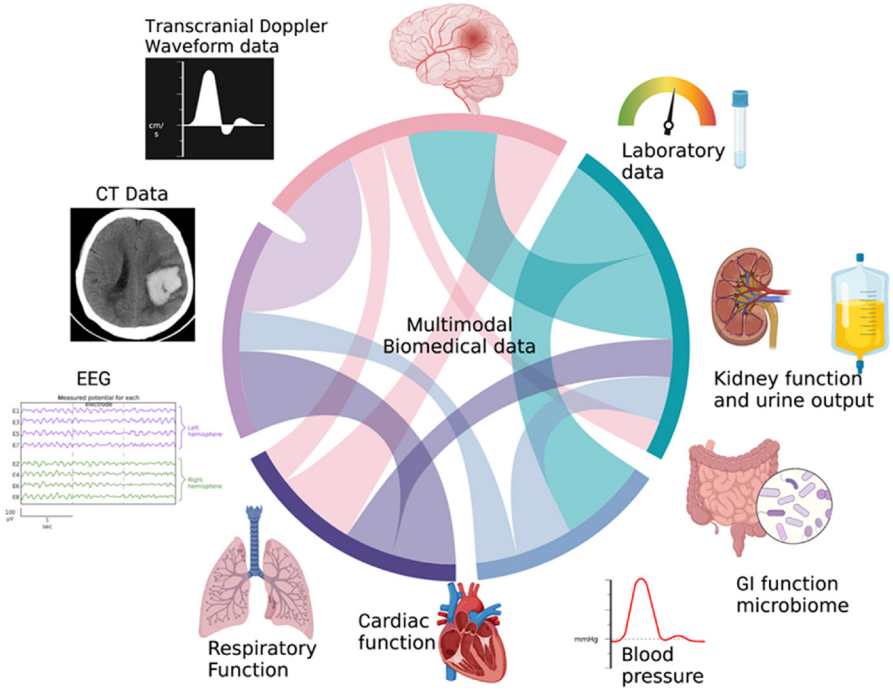

Fig. 2. Cord diagram showing AI-based integrated multimodal biomedical information utilizing multiparameter brain data as well as other ICU physiologic data. (Created in BioRender. Freeman, W. (2024) BioRender.com/u32f974.)

AI can aid in training robotic interventions for increased precision in a timely manner.[60,61]

ARTIFICIAL INTELLIGENCE IN MEDICAL EDUCATION

Medical knowledge keeps growing exponentially, and AI must play a critical role in the future. This task is not an easy one and there needs to be a balance between augmentation of learning and overreliance on AI technology for personal education. AI can potentially broaden and facilitate the training of clinical medicine a but can also lead to loss of understanding of crucial concepts which are required for understanding of human physiology as well as management of emergent issues at bedside. The loss of cognitive effort in learning risks, loss of learning altogether leading to a dearth of intuitive and innovative thinking, the type of thinking that has shaped this profession over centuries. There is also a challenge of maintaining academic standards as students have access to LLMs like ChatGPT which can be used to complete assignments. LLMs have been shown to get passing grades in the US medical licensing examination as well as mock boards for Neurology.[55,62] Discerning limits to utilization of these models in education is a great challenge for educators, schools, and governing bodies like the Accreditation Council for Graduate Medical Education. The amalgamation of AI with medical education is inevitable and will shape the future of clinical practice but there needs to be intensive research into the methods of its incorporation and its effects on all facets of medical education.

INNOVATIONS AND CHALLENGES

AI–ML and DL models may open up a new frontier of personalized treatment and precision medicine for neurocritical care patients and providers. Real-time multimodal patient data, however, could be used to generate predictive models and avoid complications. Such AI–ML models could also be used to individualize drug-dosing, point out drug–drug interactions similar to informatics models, and help recognize subtle patterns in data to make diagnostic and therapeutic suggestions. AI-powered teletriage systems could also help neurointensivists at a distance by using neuroimaging across large geographic areas, which would help provide access to underserved populations in regions with limited resources. AI–ML also has great potential to impact neurologic care by facilitating drug discovery.[63,64]

However, many challenges lie ahead before these models can reach safe widespread use, such as overcoming barriers to adoption and learning, costs of education and implementation in hospitals, and reluctance of health care systems and patients themselves. There are currently no laws in the book regulating AI. Also, there does not exist a common code of ethics regulating AI. The 3 laws of robotics devised by Isaac Asimov and its derivation are often cited as guiding principles for AI, but these are merely hypothetical concepts without real-world iterations.[65,66] Ethical AI and regulatory frameworks are emerging including the executive office of the President about the use of ethical AI for the common good and safety of humankind.[67]

Disparities in access to AI-based systems may exacerbate the existing disparities in health care. Communities with limited resources will likely end up at the forefront of these disparities. Given all AI systems are trained on preexisting datasets, AI systems may perpetuate biases incorporated into those datasets unless measures are developed to prevent this from happening.[68,69] It is imperative that a regulatory framework is established at least for the implementation of AI systems in medicine that ensures transparency, accountability, and equitable access to these systems and applications.

SUMMARY

The promise of AI in Medicine is great and has immense potential to transform the practice of medicine. It can revolutionize the world of clinical research allowing us to see beyond the obvious, hasten discovery of disease processes, new biomarkers, and potential treatments for disease. It can facilitate faster and prompt treatment of medical emergencies and facilitate individualized care for patients. It can extend the prompt reach of specialists beyond the conventional geographic boundaries, at the same time reducing the burden and burnout of practitioners. It will change the paradigm of medical education and medical ethics. However, the road to this future will be arduous and full of challenges. The medical community will need to keep command of this change, lest we fall behind the pace of evolution and allow it to run amok without direction or purpose.

DECLARATION OF AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors disclosed the utilization of a generative AI tool (ChatGPT) to aid in rephrasing English content within this article but not primary authorship. They acknowledged that ChatGPT was not employed to generate any conceptual material in this study. Furthermore, all rephrased sections produced by ChatGPT were reviewed carefully by the authors to ensure the absence of any misrepresented information.

CLINICS CARE POINTS

- Pearl: AI-powered continuous EEG monitoring can improve the detection of non-convulsive seizures in critically ill patients, potentially leading to earlier intervention.Pitfall: Over-reliance on AI systems may lead to missed atypical seizure patterns that require human expertise for interpretation.
- Pearl: Machine learning algorithms can predict the likelihood of cerebral vasospasm in subarachnoid hemorrhage patients, allowing for proactive management. Pitfall: Current predictive models may not account for all patient-specific factors, necessitating careful clinical correlation.
- Pearl: AI-assisted imaging analysis can expedite the identification of large vessel occlusions in acute ischemic stroke, potentially reducing time to thrombectomy. Pitfall: The accuracy of AI systems may vary depending on the quality and type of imaging modalities used, requiring standardization across centers.
- Pearl: Automated pupillometry combined with machine learning can provide early warning signs of increasing intracranial pressure. Pitfall: Environmental factors and patient characteristics can affect pupillary measurements, necessitating careful interpretation of automated results.
- Pearl: AI algorithms can assist in predicting outcomes after traumatic brain injury, aiding in clinical decision-making and family counseling. Pitfall: Current prognostic models may not capture the full complexity of TBI recovery, and should not be used as the sole basis for limiting care.
- Pearl: Machine learning-based analysis of multimodal monitoring data can identify patterns predictive of delayed cerebral ischemia in SAH patients. Pitfall: The integration of multiple data streams requires robust IT infrastructure and may be challenging to implement in resource-limited settings.
- Pearl: AI-powered clinical decision support systems can help standardize care protocols and reduce variability in neurocritical care management. Pitfall: Over-adherence to AI recommendations may lead to a decrease in individualized patient care and clinical judgment.

- Pearl: Natural language processing of electronic health records can identify patients at risk for delirium in the neurocritical care unit. Pitfall: The accuracy of NLP systems depends on the quality and consistency of clinical documentation, which can vary significantly between providers and institutions.
- Pearl: Machine learning models can predict the need for neurosurgical intervention in patients with traumatic brain injury based on initial presentation and imaging. Pitfall: The decision for surgical intervention involves nuanced clinical judgment that may not be fully captured by current AI models, necessitating expert neurosurgical consultation.

DISCLOSURE

The authors have nothing to disclose.

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